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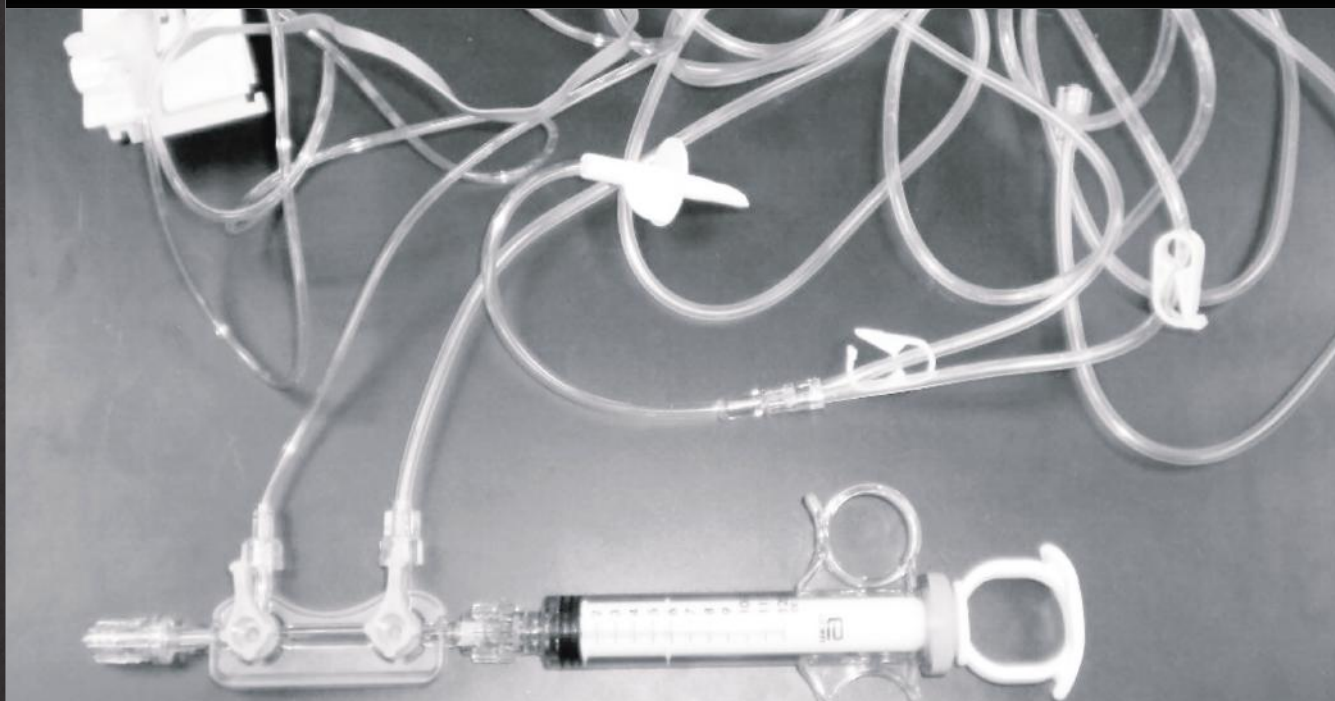
THIRD EDITION

DESIGN OF BIOMEDICAL DEVICES AND SYSTEMS

Paul H. King • Richard C. Fries • Arthur T. Johnson



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To

Sue

my wife and best friend

Paul H. King

To my wife

June

whose friendship, support, and love

make me whole

Richard C. Fries

and

In appreciation for the special people in my life who have greatly helped me to get this far.

Arthur T. Johnson

Contents

Preface

The design and functional complexity of medical devices and systems have increased during the past 50 years, evolving from the use of a metronome circuit for the initial cardiac pacemaker to functions that include medical bookkeeping, electrocardiogram analysis, delivery of anesthesia, laser surgery, magnetic resonance imaging, and intravenous delivery systems that adjust dosages based on patient feedback. As device functionality becomes more intricate, concerns arise regarding efficacy, safety, and reliability. Both the user and the patient want the device to operate as specified, perform in a safe manner, and continue to perform over a long period without failure. To be successful, the designer of medical devices must ensure that all devices meet these requirements.

Medical device design is a complex process that requires careful integration of diverse disciplines, technical activities, standards, regulatory requirements, and administrative project controls. The need for systematic approaches to product development and maintenance is necessary to ensure a safe and effective device for the user and the patient, an economical and competitive success for the manufacturer, and a reliable, cost-effective investment for the user.

This third edition of the book is aimed generally at senior bioengineering students who are in the formative stages of deciding what to do for a senior design project and who need to consider what the societal factors are that may or may not impact their project now or in the future if brought to a useful conclusion. Portions of the book may be used in lower level classes, such as the sections on brainstorming and elementary idea generation techniques. Portions of the book may be used in early graduate level classes if one has had little exposure to the Food and Drug Administration (FDA) and CE mark information. The book is meant to be fairly comprehensive, so that the needs of a variety of students working on a variety of topics (from databases to process analysis to device improvement) may have adequate information to begin a fairly comprehensive project. Additionally, it is aimed at design engineers new to the medical device industry who have not had access to such a comprehensive book or course in their background. This book should prove to be an excellent resource for those individuals as they enter the workforce.

The emphasis of the book is on the practical, hands-on approach to device design. The layout of the book follows the typical design process. The mathematics included here is that which is necessary to conduct everyday tasks. Equations, where needed, are merely given, not derived. It is assumed that the reader has a basic knowledge of statistics. References are given at the end of each chapter for those wishing to delve more deeply into the subject.

The first three chapters are a general introduction to the subject. Chapter 1 introduces the reader to biomedical engineering design. Chapter 2 is an outline of some fundamental ideas, generation techniques, and design decision and comparison tools with a brief introduction to the process of inventive (TRIZ) problem solving. Fundamental to successful design processes is the generation of a good design team and the management thereof; this is introduced in Chapter 3. This section then naturally sequences into the need for documentation techniques and requirements, and the use of databases in this endeavor. Reporting techniques are briefly covered in discussion on posters, oral presentations, and progress reports.

Fundamental to a good design is correct and customer-driven product definition. Chapter 4 summarizes the product definition process, and reiterates and concludes on the use of QFD in this process.

Product documentation, record keeping, and levels of effort mandated by FDA quality regulations and medical device regulations are discussed in Chapter 5.

Chapter 6 gives an overview of hardware and software design techniques that ensue from the earlier product specification tasks. Specifically covered is the FDA concept of the product development

process, which outlines the links from product requirements to design transfer, with intermediate links such as design verification and validation.

Hardware development methods and tools are reviewed in Chapter 7. Overviewed are such topics as design for Six Sigma, robust design, failure modes and effect considerations, axiomatic design, design improvements via component derating, reliability prediction and improvement, and several design for "X" methodologies. The chapter concludes with a discussion of design reviews.

Chapter 8 is an introduction to software development methods and tools. Because software differs from hardware, methods and tools used for software development are very different from those used in hardware development, but constraints on verification and validation as mandated by the FDA are paramount.

Chapter 9 overviews human factor issues. Several of the techniques used to guard against human-caused errors are reviewed, as are techniques to increase usability. Workstation design and human expectations are also discussed, as are the methods used to test these in use.

Chapter 10 discusses industrial design, including developing user interface concepts, designing a conceptual model, developing screen templates and a screenplay, and testing the design.

Biomaterials and materials selection are the theme of Chapter 11, with heavy coverage of the various FDA (and some international) tests and test methods used for materials that may come into contact with users. Tests for toxicity, hemocompatibility, irritation, reactivity, and sensitization are summarized.

Chapter 12 covers risk analysis of devices and systems, including some safety topics not dealt with elsewhere in the text, specifically addressing safety as a component of the design process and one of several structured approaches to the consideration of safety in a design.

Once the design is completed, it must be tested to prove whether it meets its requirements. The subject of testing is summarized in Chapter 13. Types of tests, parsing test requirements, establishing a test protocol, and defining failure are all discussed in detail. The chapter also discusses the methodology for determining test sample size and test length.

Once the testing is completed, the test data must be analyzed to determine the success or failure in testing. Chapter 14 explains the mathematical basis of analyzing test data. Metrics that are covered here include failure rate, reliability, mean time between failures, confidence level, confidence limits, and minimum life. There is also a discussion of graphical analysis of data, including Pareto charts.

Chapter 15 discusses the legal ramifications of medical device development and failure. Topics include negligence, breach of warranty, failure to warn of dangers, accident reconstruction, and forensics.

Chapter 16 discusses the FDA and its role in the regulation of medical devices. Device classification, manufacturer registration, and types of registration and listing are among the topics discussed.

Chapter 17 discusses FDA history and relevant nondevice regulations. A comprehensive history of the FDA is followed by a discussion of drug enforcement and postproduction oversight and enforcement.

Chapter 18 discusses biological engineering design. The emphasis of the chapter is on biological systems impacted by engineering.

Chapter 19 discusses international regulations and standards. Medical devices sold in the United States must meet FDA regulations and US standards. Those devices sold in other parts of the world must meet regulations and standards from those areas where they will be sold.

Good design will likely generate intellectual property. Chapter 20 gives a summary of the protection of intellectual property, including licensing, patents, copyrights, and trademarks.

Chapter 21 covers manufacturing and quality control. This chapter discusses manufacturing processes and how quality control issues continue during this phase of the design process and how they must be addressed.

Chapter 22 covers a few miscellaneous issues not relevant to other chapters, specifically such issues as learning from failure and designing for failure.

Chapter 23 is a brief synopsis of professional issues that must be considered by the biomedical professional. Specifically, membership in professional societies, licensure, and professional ethics are discussed. Forensics and consulting are also briefly covered.

Chapter 24 is essentially a resource chapter. It is written to assist and advise you, the reader, in determining if you wish to take your concept as developed in your coursework, profession, or otherwise to a point where you decide to develop your final product.

Design of Biomedical Devices and Systems, 3rd edition, is the joint effort of three engineers, one with more than 40 years of teaching and research experience in biomedical engineering and 20 years as the sole instructor of a senior design course (King), another with more than 30 years of experience as a reliability engineer in the biomedical device industry (Fries), and the third with 34 years of experience in the department of bioengineering (Johnson).

With the publication of the third edition, the authors felt that an explanation of the history of this book might be in order. As such, the normal place for a history is here.

In 1991, author King was assigned the task of initiating the first required one-semester senior design course at Vanderbilt. With only a semester for lecturing and for project work, the didactic material for the course had to be very limited and was fairly much constrained to a quick overview of "who, what, where, why, and when"; a quick overview of codes; some discussion of the mechanics of generation of design projects; and requirements for completion of design projects.

Attendance circa 1993 at an National Science Foundation (NSF)-sponsored design teaching seminar based largely on the text by Pahl and Beitz (titled *Engineering Design, A Systematic Approach*) assisted in the formalization of the course as a structured lecture and design course with specific deadlines and requirements based upon the mechanistic approach advocated by Pahl and Beitz. This was especially helpful as by 1997, the course evolved into a two-semester sequence with the dropping of a local requirement for a database course. Given the extra time, roughly the first third of the course year became formal instruction from notes, and the latter two-thirds became design projects with weekly written and monthly oral reporting requirements.

In 1999, author King reviewed author Fries's textbook *Reliable Design of Medical Devices* for the *IEEE Engineering in Medicine and Biology Magazine*. He was impressed enough with the industrial material in the textbook to adapt the text for a period of 3 years while authors King and Fries worked on the first edition of this text and tested it on the Vanderbilt classes. The first edition of this text was published in 2002, the second in 2009. The texts are currently being used for senior design courses both in the United States and overseas.

In 2011, King reviewed author Johnson's textbook *Biology for Engineers*. The application of engineering design principles to problems in biology was an aspect of our editions that author King felt was lacking in the early editions. As a result, author Johnson was cajoled into adding a chapter on biological engineering design to this textbook in order to broaden the horizons of students who may work not just in the medical domain but also in the biological domains not previously covered.

Johnson also relied on his 35 years of experience in teaching a transport processes design course to biological engineers at the University of Maryland. His book entitled *Biological Process Engineering* that he developed for the course has many examples from multiple applications areas in biological engineering. It is from this course that he has selected many of the design examples used in this text.

Paul H. King
Richard C. Fries
Arthur T. Johnson

Acknowledgments

We are deeply indebted to many people for their encouragement, help, and constructive criticism in the preparation of this book.

Author King wishes to thank his coauthors, the over 1200 students who have suffered through his lectures and who have performed over 500 projects in the 20-year history of his teaching engineering design in the Department of Biomedical Engineering at Vanderbilt. He wishes to thank the other (EE, ChE, ME) design instructors at Vanderbilt for their camaraderie and sharing of students on projects (both ways). He also wishes to thank others who have contributed in reviews and additions to various chapters and those who have contributed in other ways (such as coworkers in anesthesiology and the lawyers who have, on occasion, presented him with interesting consulting cases, some of which are presented here). Thanks also to the NSF and National Collegiate Inventors and Innovators Alliance (NCIIA) for support of the course and projects and to CRC Press/Taylor & Francis for publishing this text.

We want to thank the biomedical engineering students in senior design at Vanderbilt University for their review and constructive criticism of the first edition of this book. Their input made this a better text. We thank those of you who have adopted and/or reviewed the prior editions also. We appreciate the feedback from faculty users that has influenced the content of this third edition.

Authors

Paul H. King, PhD, PE, attended Case Institute of Technology for his BS and MS degrees and then obtained his PhD at Vanderbilt University in 1968 (mechanical engineering.) That same year, he became one of the founding members of the Department of Biomedical Engineering at Vanderbilt University. He was department chair/program director shortly thereafter for a period of 5 years. With the exception of a 1-year sabbatical at Oak Ridge Associated Universities, he was actively teaching and doing research and service in the department until approximately December 2011. Research endeavors included work in nuclear medicine, cardiology, orthopedics, urology, and anesthesiology (19 years). He developed and taught most of the early required coursework in the Department of Biomedical Engineering. In approximately 1991, he initiated the current senior design sequence in biomedical engineering; an accompanying senior design seminar for most majors was initiated in 2001. He was exclusive instructor of the biomechanical engineering (BME) design course for a period of 20 years. In approximately 2001 he and coauthor Richard Fries published the first edition of the textbook *Design of Biomedical Devices and Systems*. This textbook is being used in multiple universities in the United States and abroad.

Dr. King has been very active in the field of design as a result of his commitment to the course and its development elsewhere. This commitment has taken the form of this textbook and of the assistance in the formation of a current enterprise termed *BME-IDEA*. The BME-IDEA group currently meets biannually and is comprised of invited chairmen and/or design instructors from universities in the United States (primarily). The meeting site precedes the Biomedical Engineering Society meeting, planning is done by an ad hoc group, and funding comes from various sources including NSF, the NCIIA, and others.

In addition to his work in the area of design, Dr. King was and remains an Accreditation Board for Engineering and Technology (ABET) evaluator for bioengineering and biomedical engineering programs. He has evaluated approximately 12 programs in the past 12 years, both in the United States and abroad. "Officially" retired in 2011, he remains active in reviewing grants and papers and is involved in design projects and in updating this textbook.

Richard Fries, PE, CSQE, CRE, is a licensed professional engineer in the state of Wisconsin and certified by the American Society for Quality as a reliability engineer and a software quality engineer. He is also certified as a Six Sigma Green Belt, an ISO 9000 lead auditor, and a TickIT lead auditor. He is trained as a Six Sigma Black Belt and a HIPAA Professional. He has degrees from Loyola University in Chicago and Marquette University in Milwaukee. He has 40+ years experience in hardware and software reliability, software development, regulatory compliance, and device design. He is coinventor of the absorber switch locking device (patent 5,682,876). He has authored eight books and chapters in several others on reliability and regulatory compliance. He has also written numerous articles in professional journals on hardware and software reliability, human factors, standards and regulations, and engineering education. He is an ABET evaluator, a senior life member of Institute of Electrical and Electronic Engineers (IEEE), a senior member of American Society for Quality (ASQ), and a member of the Biomedical Engineering Society. He is a member of the IEEE Software Engineering Subcommittee. He was a member of the Association for the Advancement of Medical Instrumentation (AAMI) Medical Device Software Committee and the Technical Committees that developed ISO 13485 and IEC 62304.

Arthur T. Johnson attended Cornell University for his undergraduate and graduate degrees. His PhD was awarded in 1969, and he immediately began serving as an officer in the US Army,

eventually serving in Vietnam at the rank of captain. He was awarded the Army Commendation Medal and Bronze Star Medal. He joined the faculty of the University of Maryland in 1975 and was professor from 1986 until 2009, when he became professor emeritus. He was cochairman of the committee to found the American Institute for Medical and Biological Engineering (AIMBE) from 1988 to 1992, and served as the executive director of AIMBE in 2004. He has been president of the Alliance for Engineering in Medicine and Biology (1984–1988), Institute for Biological Engineering (1998), and International Society for Respiratory Protection (2004–2006). He was the Secretary of the Biomedical Engineering Society from 2004 to 2009. He has been on the board of directors of the American Society for Agricultural and Biological Engineers (1995–1997). He is a founding fellow of the AIMBE (1992), life fellow of the American Society for Engineering Education (1996), life fellow of the American Society for Agricultural and Biological Engineers (2002), fellow of the American Industrial Hygiene Association (2005), fellow of the Biomedical Engineering Society (2005), fellow of the Institute for Biological Engineering (2009), and the life fellow of the Institute for Electrical and Electronics Engineers (2010). He is a member of the honor societies Phi Kappa Phi, Sigma Xi, Tau Beta Pi, and Alpha Epsilon. He has written three books: *Biomechanics and Exercise Physiology: Quantitative Modeling*, *Biological Process Engineering*, and *Biology for Engineers.* His research interests are human performance wearing respiratory protective masks, respiratory mechanics and measurement, and transport processes. He has been most recently active in teaching electronic design, transport processes, and engineering in biology courses, and in working to continue development of the airflow perturbation device as a noninvasive measurement of respiratory resistance.

1 Introduction to Biomedical Engineering Design

Give a man a fish; you have fed him for today.
Teach a man to fish and you have fed him for a lifetime.

Author unknown

This text is designed to cover the design of biomedical engineering devices and/or systems. It is intended as a reference to guide your and your classmates' thoughts and actions in design. It is based upon the authors' experiences in industry with the practice of engineering design and the authors' experiences and those of their students (both undergraduate and graduate) in the learning of design and the initiation of design projects from a multitude of sources. Also covered will be topics of relevance from the authors' experiences in court with device and process failures. With your prior instruction in engineering, with your projects of interest, it is anticipated that this text will be of value to you in the initiation and potential completion of a design project relevant to this field.

What is relevant to this field? Biomedical engineering can be very broad in scope, dependent on interests and circumstances. Biomedical engineers are expected to have some familiarity with medical devices, their design, their regulation, and use. They are further expected to consider safety aspects of the devices and should consider the potential misuse of a device. Designers may be expected to involve themselves in the improvement of a process, such as the processing of patients in a hypertension or cancer clinic. They may get involved in biotechnology to manufacture products derived from mammalian cells; they may wind up in the manufacturing of implant devices for the treatment of diabetes. They may design a specialized brace for a single individual or design a medical device to be used by thousands of patients. It is vital to understand the many meanings of the term *design* and have some experience at problem solving using the design principles and other considerations to be outlined in this text.

1.1 WHAT IS DESIGN?

It is useful to discuss design from two viewpoints this early in the text, first by discussing what it is not and then by discussing what it is and the many forms of it.

Design is not research, which may be defined as "a careful investigation or study, especially of a scholarly or scientific nature."[1] A design task may require research to accomplish a task, but it typically involves the integration of knowledge rather than the generation of knowledge. Research may be done into the process of design and, as such, is sponsored by such groups as the National Science Foundation (NSF) (see http://www.eng.nsf.gov/dmii/index.htm for the design, manufacturing, and industrial innovation research division). A researcher (scientist) may study nuclear fusion, but an engineer (designer) must be involved in the construction of a nuclear power plant.

On the other hand, design is not craftsmanship. Designers are not nor should they be viewed as craftsmen. This work will involve brains and skills, not just skills.

Design as an action verb is

- To conceive, invent
- To formulate a plan for; devise
- To have as a goal or purpose; intend[1]

Design work thus does not necessarily involve the manufacture of a physical device; it can be a plan or process, or a study to determine the same. Naturally, it can range from this level to the complete specification of a device and its manufacture.

Design as a noun (thing) incorporates the following:

- A drawing or sketch, especially a detailed plan for construction or manufacture
- The purposeful arrangement of parts or details
- The art or practice of making designs
- An ornamental pattern
- A plan or project
- A reasoned purpose; intent
- Often a secretive plot or scheme (Latin)[1]

Each of these terms has validity in the types of work that will be discussed in this text, especially if the device is useful and novel, and therefore potentially patentable. Even the ornamental pattern qualifies as it is a product of the intellect, is therefore an invention, and may qualify as patentable intellectual property. How does a secretive plot qualify? Perhaps under the category of "trade secret," for example, is the recipe for the manufacture of Coca-Cola.

1.2 WHAT IS THE THRUST OF THIS TEXT?

This text is aimed at introducing one to the application of design processes to a wide category of design problems in biomedical engineering. It is anticipated that the user of this text will be involved, during the reading of this text, in one or more design projects and/or exercises. It likely will best be used in parallel with some early design exercises and then referred to occasionally as a major design project is pursued. It is meant to be a part of the learning triad of hear/see/do but not all of it.

The text also attempts to place the various steps in the design process in a logical order, typically that followed in engineering best practices for conducting and completing a design project. The process is generic and flexible, so that processes may be included or not, depending on the project.

1.3 WHAT MIGHT BE DESIGNED?

A partial listing of senior-level (and some graduate-level) design projects follows.

Biomedical devices:

- Modified patient brace for an individual
- Patient (for example, Alzheimer's) (or pet) tracking device
- Development of a hand exerciser
- Improved safety warning system for an intensive care unit
- Improved patient monitoring for premature infants
- Development of a voice training system for patients with Parkinson's disease
- Development of a surgical tool for use in spina bifida surgery
- Development of an adjustable tray for a spinal cord–injured patient

- Modification of a riding mower for use by a paraplegic
- Development of a laser spot size measurement system for use in throat surgery

Biomedical systems:

- Improved patient record-keeping system for a perioperative surgical unit
- Revised and improved vaccine database system
- Comprehensive pain clinic data collection/billing system
- Development of a prostate cancer screening test
- Development of a skin disease database
- Development of a research ward database system
- Improved feeding apparatus for cystic fibrosis patients
- Development of a device for laparoscopic band pressure regulation
- Biofeedback system for wheelchair propulsion systems
- Development of a cauterizing biopsy catheter
- Development of a drug-eluting stent

Biomedical processes:

- A study of patient flow in an emergency room
- Improved patient communication in a breast cancer clinic
- A determination of clinic space and facility needs
- Development of a system to measure foot impressions and transmit same
- Optimization of T-cell trapping in a microfluidic device

Note the key words *improve*, *develop*, *revise*, and *study*. Note also the key words *device*, *process*, and *system*. Each of these terms will see major elaboration in the ensuing chapters. Design will, on occasion, involve invention but generally will involve an application (extension) of existing technology. In addition, as will be noted in the solution of design problems, there will be no "exact answer," but instead, there will be best attempts given constraints involving timing, financing, and so forth of project work.

1.4 THE ESSENTIALS OF DESIGN—OVERVIEW

A well-written newspaper article quickly answers the following questions: Who? What? Where? When? Why? How? The process of design typically involves such considerations, with the addition of decision points in the design process as outlined in Figure 1.1. The generic design process, the flowchart on the left-hand side, outlines the process from design task initiation (from whatever source) to task completion. The center section outlines the process of task clarification, the search for solutions and evaluations of same, and the generally necessary reiterations of same until an acceptable solution is reached.

On the right-hand side are listed the who/what/why/when/where/how questions normally asked at each phase, with the addition of the go/no decision part. The most critical part of this listing is the initial "what?" elucidation—if the design task is not adequately described at the outset, the entire process from then on is generally wasted time and money! If one properly defines the problem (i.e., understands the who/what/why/when/where part), then one can hope for a tracing directly to the solution evaluation section. If the solution is wrong, *or* if the problem definition is wrong, one will have to backtrack and rework the overall solution. The most vital part of the design work will be to figure out what it is that one is asked to do.

Part of this problem will hopefully be minimized by your (and/or your team's) prior educational experiences, which should have included medical nomenclature, some systems physiology, and

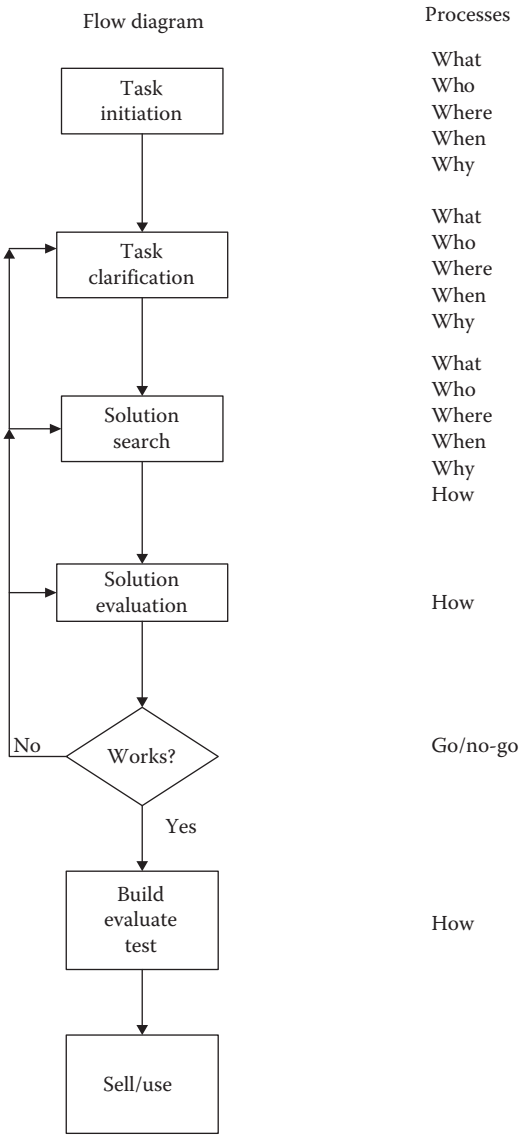


FIGURE 1.1 A generalized flowchart for the design process.

medical instrumentation. If one is working with a nonengineer on your design project, some new communication skills may be needed. This will be especially true in dealing with most physician collaborators, who commonly go from diagnosis to treatment (or therapy) on a generally nonmodifiable patient, while the designer is charged with the modification of a device or process.

1.5 BIOMEDICAL ENGINEERING DESIGN IN AN INDUSTRIAL CONTEXT

Figure 1.2 is a concept map[2] describing, in a hierarchical fashion, the overall elements of the biomedical engineering design process in the context of society. It is a consensus document as to the generic elements that must be considered in the overall design process. To understand this system, one normally would read from the top down and from left to right.

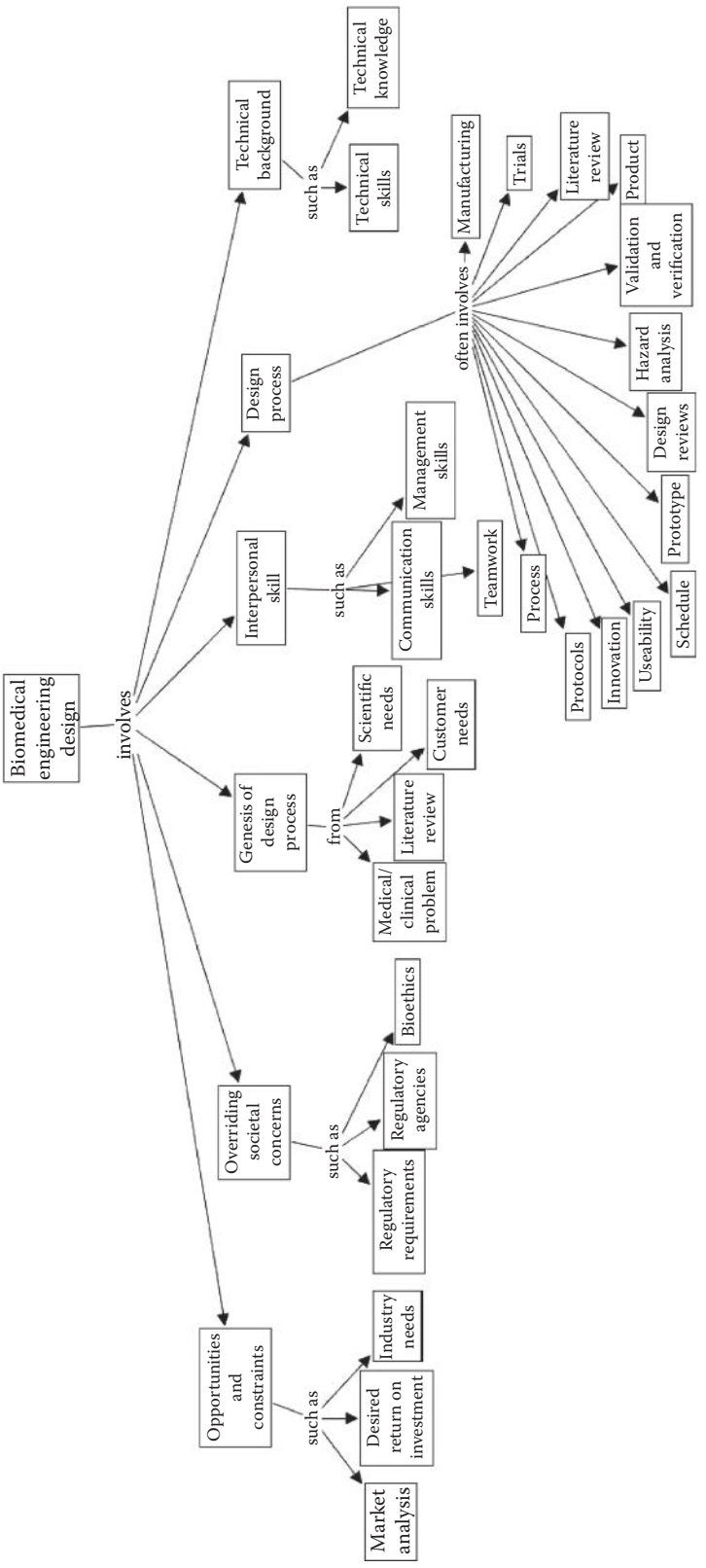


FIGURE 1.2 The generic biomedical engineering design process.

Biomedical engineering design projects generally involve opportunities, subject to certain constraints. A company will not typically pursue a project unless a market analysis has been done, there exists a potentially desired return on investment, and/or the product is a fit with industry needs (and intellectual property rights may be retained). (In contrast, for a student design process in a generic academic setting, projects are generally proposed to students based upon the potential advisors' [medical faculty, engineering faculty, industry advisor] needs, tempered by what might be expected from a student design team, etc.)

For industry, there are several overriding societal concerns involved in the design of devices and products; these involve multiple regulatory requirements (licensing, waste disposal, liability issues, etc.); regulatory agencies (the Food and Drug Administration [FDA], etc.); and bioethical constraints (animal care rules, human subjects committee approvals, etc.). (For student projects, human subjects committee approvals are sometimes necessary, a knowledge of FDA rules is useful, a project may brush with the group Persons for the Ethical Treatment of Animals [PETA], etc.)

Design projects typically arise from studies of medical and clinical problems (such as device complaints), a literature review, the scientific project needs of clinical and academic investigators, and occasionally, the needs of individual customers.

Design projects seldom involve a single designer, and thus, issues of interpersonal skills, such as communication skills, management skills (especially time management), and teamwork skills, come to the forefront of the design process.

The design process itself may involve developing a process (as opposed to a device). The industry design process will often involve development of manufacturing methods and testing of devices in trials according to specific protocols. Devices and processes must be tested for usability. Specific schedules must be developed in order to keep a competitive edge. Periodic design reviews are mandated to maintain schedules and to determine validity and verification of the design. Hazard analysis should be done as a product is being developed, rather than later, when liability becomes an issue. If possible, a prototype of the device or process should be developed and used for testing purposes prior to final manufacture of a product.

Design teams typically require technical skills and knowledge from a variety of disciplines; this is normally accomplished by the generation of multidisciplinary design teams. Dependent on the particulars of a problem, the engineering team should include a required mix of electrical, mechanical, biomedical, computer, and chemical engineers. Persons with these backgrounds, as well as with an engineering management background, might form the core of the engineering product development team. Manufacturing and industrial management engineers may or may not be included in the prototyping or concept development team but will be needed in the manufacturing part of the overall development.

1.6 AN OVERVIEW OF THE INDUSTRIAL DESIGN PROCESS

Figure 1.3 is a combined concept map/flowchart overview of the process industry uses in the design of relevant products as outlined by author R. Fries. An understanding of this chart will prepare the reader for the remainder of this text and the reasons for the breadth of material covered.

Design ideas/projects in the biomedical industry come largely from clinician feedback and an examination of competitors' products; brainstorming is used as a generic tool in the initial phases of team designs of prototypes. Prototypes (occasionally simply mock-ups) are examined for financial and design feasibility and often scrapped prior to major investment.

A "go" command will generally involve the initiation of multiple activities, such as the formation of design teams with specific subtasks, detailed design specification generation, development and establishment of timelines, initiation of user and technician manuals, and initial design activities, especially those involving the development of submodules, testing of components, safety testing,

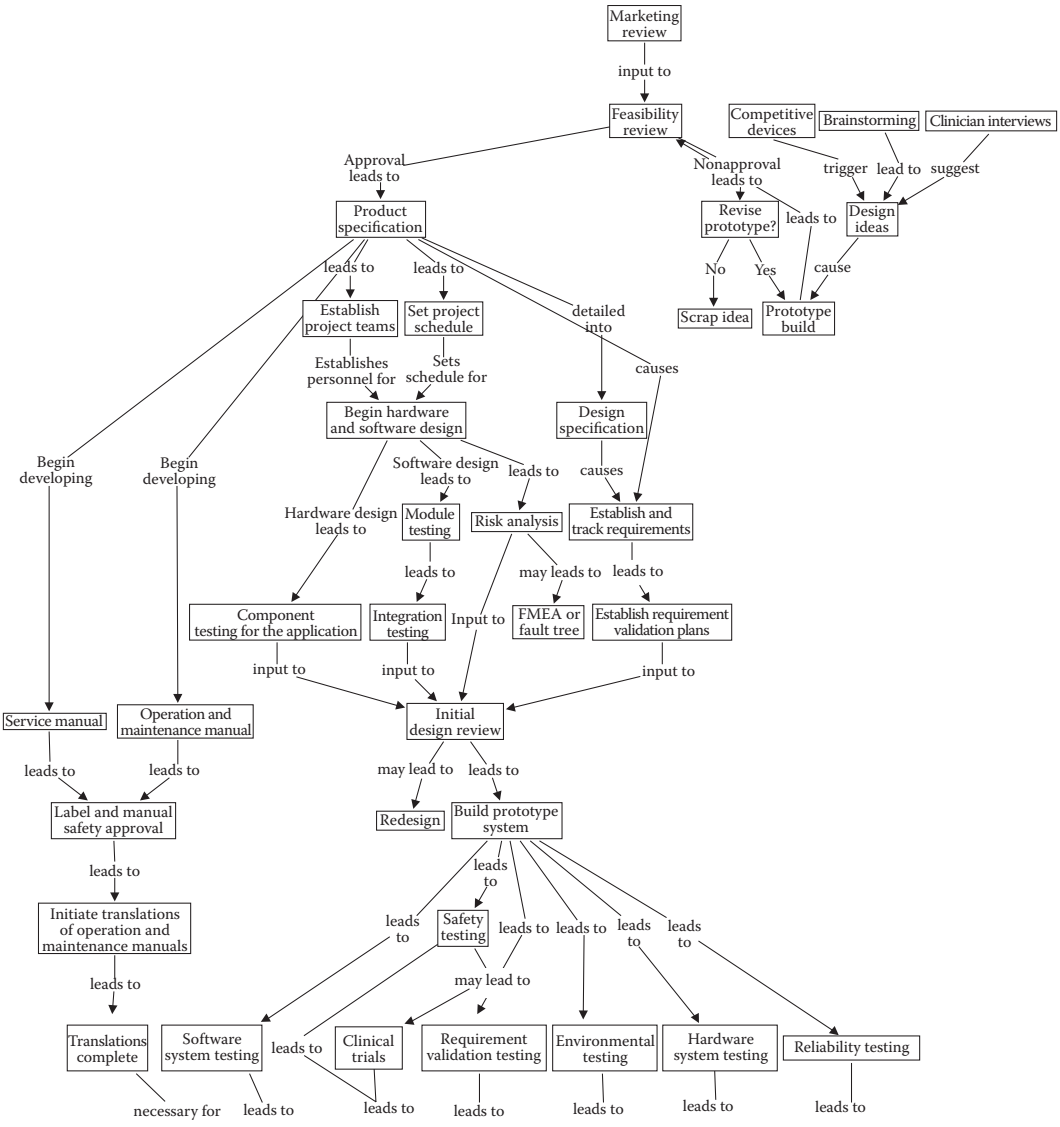


FIGURE 1.3 Industrial design flowchart.

and monitoring of adherence to standards. Failure modes and effects analysis (FMEA) and other fault analysis studies must be done. An initial design review serves as a go/no-go/redesign "gate."

Periodic design reviews serve as continue/quit/redesign decision points for the simultaneous design activities of environmental, reliability, hardware and software, and safety testing activities as the prototype system is being developed.

Typically, a final design review will (hopefully) initiate transfer of responsibility to the manufacturing component of the company and simultaneous marketing activities and US and international regulatory requirement satisfaction. If all goes well, and regulatory and manufacturing and marketing requirements are met, the device will go to production and then to market.

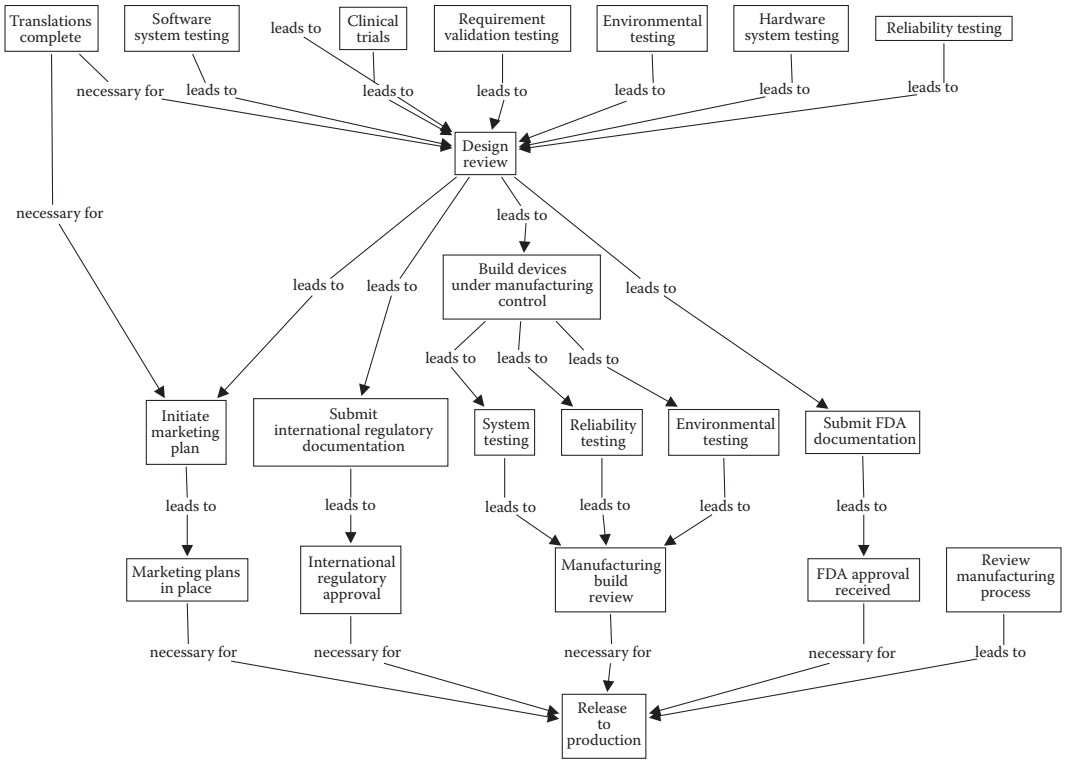


FIGURE 1.3 (Continued) Industrial design flowchart.

1.7 HOW THIS TEXT IS STRUCTURED

This remainder of this text will approach the process of design as generically as possible; the special constraints relevant to biomedical engineering will be added as necessary. The topics outlined in the previous discussion of the generic industry design process will be covered. Additional coverage will be added to acquaint the reader with specific details regarding professional and ethical issues. A concluding chapter is included to assist you in the event that you wish to continue your design work in this field. Interspersed in the chapters will be relevant design examples from your authors' industrial and academic careers.

1.8 THE REAL PURPOSE OF THIS TEXT

The real purpose of this text is to guide one in the tackling of a real-world design task relating to biomedical engineering. It is meant to be supportive of the newly involved engineer in the medical device market. It is meant to prepare bioengineering and biomedical engineering students for development of senior design projects (primarily) and for careers in the medical device development industry. An ultimate goal is to prepare one for a career in design as advertised in the following web-based example advertisement (2000):

> R&D Engineer: This position offers excellent growth opportunities for the highly motivated individual. Seeking engineer to assist our product development team in developing and testing proprietary medical device concepts. Candidate must be hands-on and able to work independently. Working knowledge of ISO and FDA requirements preferred. Principle responsibilities will include product design, testing,

and analysis. Qualified candidate should have 1–3 years' experience with medical device company and BS in mechanical engineering, materials engineering, or biomedical engineering. Additional responsibilities may include animal testing, clinical evaluation, patent/literature searches, and support of ongoing development projects as required. Experience with biomaterials and mechanical design a plus."[3]

This, in fact, was an advertisement that a student from the class of 2000 applied for and accepted.

1.9 CASE STUDY

An overriding concern in biomedical device and process use is safety. This particular example has been used in introductory lectures in design of biomedical devices and systems as an example of multiple errors/oversights causing a patient death during an evaluation of a patient for cardiac surgery. In author King's classroom, the lecture begins with students being able to handle the following: (1) a manifold used in cardiac catheterizations (photograph, Figure 1.4), (2) one or more 1 L saline (or similar)–filled infusion bags, and (3) an opaque latex pressure augmentation bag that slips over the bags used in infusions (pressurizable via a hand pump).

The manifold (as seen in the figure) allows the interconnection of several elements. On the left side of the figure, there is a connection port for a cardiac catheter. In this particular case, the other end of this catheter was inserted (as is fairly normal for this study) through an incision in the femoral artery and threaded into the patient's heart. The port on the upper left connects (if the valve below it is opened) to a pressure gauge; under normal conditions, this allows the recording of the pressure at the tip of the catheter. The valve on the right allows connection to the infusion bag (to allow saline to flush the catheter) or connection to the ~12-mL-capacity syringe to allow sampling of fluids withdrawn from the catheter or neither. The opaque pressurization bag was pressurized (per physician's request) to allow a rapid flush of catheter contents (as opposed to simple height pressurization of the infusion solution per density times gravity times height differential).

The patient in question was a young child with multiple heart defects (atrial-ventricular [A-V] and atrial-atrial [A-A] shunts). The purpose of the study was to determine the amount of shunting in the heart in order to determine the likelihood of survival after surgery for septal defect closures. In order to estimate this likelihood, the surgeon in question needed to know the amount of shunting between various parts of the heart; to determine this the surgeon needed blood samples from each

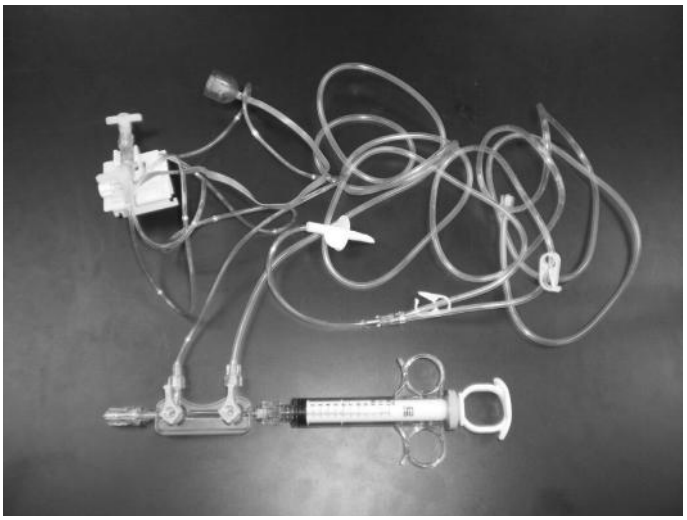


FIGURE 1.4 Manifold used in case study.

chamber, and major blood vessels, in order to determine the relevant oxygenation levels needed in this calculation.

Data collection in this case is fairly straightforward. The surgeon inserts and positions the (primed) catheter. Blood pressure recordings will indicate the pressure waveform in the catheter; this will normally reflect the pressure at the tip of the catheter, with the exception of instances of rapid infusion or sampling. When a site is reached for sampling, the physician can request a brief infusion of fluid from the infusion bag followed by a closure of the infusion. The sampling syringe may be "pulled" until blood is ready for entry to the syringe. The port then may be closed and the syringe emptied and returned, then used to pull a sample to be sent to the laboratory for analysis of oxygen levels. The syringe is then reinserted in preparation for a new sample.

In this particular case, the study of the patient went normally for about an hour. Blood pressure waveforms were continuously recorded and had been normal for this patient (as had a separately acquired electrocardiogram) until quite some time into the study, at which time the pressure waveform became erratic and very low amplitude (similar to what you might imagine static to look like). Once seen, this pattern is not to be forgotten; it is indicative of an air embolism in the heart. With air in the heart, bubbles form, and despite the best efforts of the surgeon and team, the patient succumbed within minutes. The case became one for investigation prior to any court actions.

The central question in this case is the following: Where did the air come from? As it caused a death, how much did it take? What steps could have been taken to avoid this in the future?

Potential sources and air were investigated (by Author King and a colleague). Suggestions typical of a class of students seeing the manifold and so forth are the following: (1) A potential source of air could have been caused by the catheter "puncturing" the heart and allowing air from the pleural space or lungs to enter the heart. Response: the catheter continued to reflect the pressure in the heart, not that of the lungs. No active forcing of the catheter was obvious in the record. (2) Air could have "leaked in" from the groin (femoral artery) insertion area. Response: to do so, air would need to be "sucked in"; otherwise, the net effect of a groin insertion problem would be bleeding out from the patient. As blood pressure was normal and the patient was supine (and thus, there was no pressure head, positive or negative, due to position), this possibility was eliminated. (3) Air leaks occurred elsewhere in the system (opening at the blood pressure gauge, for example), causing air to flow in. Response: As air had to enter at greater than systolic blood pressure, no such air "leaks" were possible. (4) The sampling syringe could have been filled with air and the air injected. Response: The 12.5 cc volume of the syringe—if filled with air and injected—*could have* caused the patient's death. The fact that no active sampling activities were documented at the time of the incident made this a less likely cause. (For a fact, however, this accidental injection of air and its consequences have been noted elsewhere.) (5) Air in the infusion bag got into the patient. Response: This was the *most likely* cause of the patient's death. The infusion bag used normally had ~35 cc of air in it. With the (opaque) pressurization bag inflated "enough," it was possible to completely drain both infusion fluid and any air in the bag! With an "opaque" bag, it is impossible to note that the "bag is almost empty" and in need of replacement (prior to potential air infusion). How could this death have been avoided? (1) Do not pressurize the infusion bag! The value added (speed of flushing the catheter) is not worth a life. (2) Put an air detector in the catheter—shut the system down if air is on its way to the patient. (3) Do not use infusion bags that have air in them!

Why is there air in the bag? To allow mixing of drugs when injected into the bag (after a good shake)! Without the air (and shake), the likelihood of a bolus of medicine (for example, morphine) rather than a well-diluted mixture of same causing problems is more likely!

To conclude this chapter, design is a process. Design involving living systems involves special considerations, which we will address in the following chapters. Paramount will be safety!

EXERCISES

1. Often, design projects are generated by persons concerned about improving the welfare of persons close to them (patients, family, friends). Think about your acquaintances and develop a design project definition that could motivate you. Be sure to detail the who/what/where/why/when/how specifics as much as is necessary.
2. An orthopedic physician has proposed that you study the effect of electrical stimulation on the healing rate of a bone fracture. Write this request up—briefly—as a research project. Rewrite this as a design project. Discuss the differences in the approaches.
3. You have done some form of design project in your personal life (device, plan of action, project, college choice, etc.). Briefly describe, for your instructor, your favorite project and any lessons learned from it.
4. This is a good time to look at your background in order to determine what areas you will be qualified to work in. What would you list as your assets in terms of your potential contribution to a design team?
5. The who/what/where/why/how/when construct is often used in newspaper writing. From your Sunday newspaper, extract one short news story and one obituary and analyze them for the above content. Turn in both articles and your commentary to the instructor.

REFERENCES

1. Microsoft Encarta Encyclopedia (CD, Microsoft Corporation), 1999.
2. Tutorial and software available from the Institute of Human and Machine Cognition, Pensacola, Florida.
3. Job opening listing, Kensey Nash Corporation, Exton, PA, May 2000. See http://www.kenseynash.com/ for current information.

2 Fundamental Design Tools

Men have become the tools of their tools.

Henry David Thoreau

There are a series of design tools in current use that will be valuable in the design process as discussed in the remainder of this text. Some of these tools will be covered on an introductory level in this chapter. As design is, in truth, an information gathering and processing activity, these tools will reflect this process. Some of the tools involve interaction with humans, some with computer programs, and some with physical devices. This text will cover solution search methodologies and function structure abstraction, including flowcharting techniques.

2.1 BRAINSTORMING AND IDEA GENERATION TECHNIQUES

Without knowledge of idea generation techniques a designer may rely too heavily on prior knowledge or on making minor adjustments to a device or process that could be dramatically overhauled. For good idea generation, one needs to be able to "think outside of the box" (of prior known solutions). Some of the more common idea generation techniques include brainstorming, Method 635, the Delphi Method, and Synectics. There are variations on the themes, as discussed later, and computer support and training tools exist for these and many other methods.

2.1.1 Brainstorming

A typical brainstorming group will consist of 5 to 15 individuals generally chosen by the person who will be the discussion leader. The individuals should consist of the design team searching for a solution and involve an additional mix of laypeople or other people who might be able to contribute due to their backgrounds. In a university environment, brainstorming teams consisting of several engineering students and two or three arts and science students are often much more effective than teams of just engineering students. The additional viewpoints are useful, as is the extra brainpower.

In preparation for the session, the leader should set a reasonable duration for the meeting (20–40 min) and stress that there will be no hierarchy and no criticism of any ideas presented. Further, no self-defeating statements should be allowed ("the boss won't allow that," "it is impossible," "not worth solving," etc.). At the outset of the meeting, the leader should state or restate the problem to be solved and reiterate the rules for the meeting. The brainstorming discussion then begins, with the leader primarily trying to maintain a flow of information from single individuals, rather than having multiple people trying to talk at once. The leader may not lead the discussion but may, during periods of long silence, suggest elaboration or expansion of earlier suggestions. All ideas are to be heard and posted, even the "ridiculous" ones, as they may, in fact, lead to a novel solution. No derogatory or dismissive comments are allowed. Someone, the leader or a designated secretary, should take minutes on the meeting. One suggested method is to write each idea on a Post-it note for later reclassification.

At the end of the session, the group can evaluate, rank, and, if desired, classify all ideas. The rank ordering and evaluation of the list then can become an agenda for the design team and its efforts. If the ideas are also classified, a design tool such as concept mapping can be used to categorize ideas and guide further work. Such a mapping for a brainstorming session on grades in a design course is illustrated in Figure 2.1. Note that the "ridiculous" ideas remain at this stage.

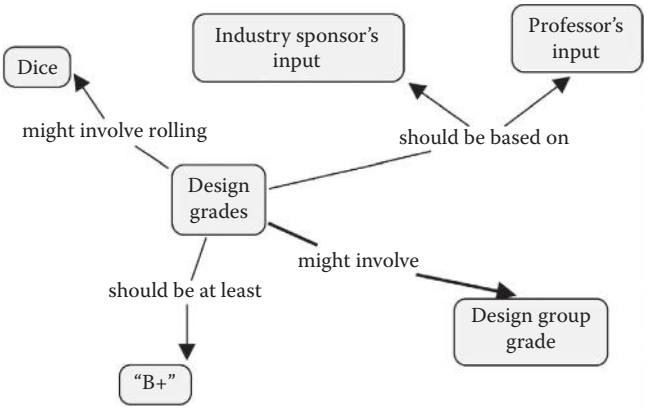


FIGURE 2.1 Concept map for a brainstorming session on grade sources in a design course.

Brainstorming is generally useful in conditions when new ideas are needed and/or when a design group is deadlocked on methods to use in a design process. A drawback is that it relies on the abilities and backgrounds of the practitioners and on their willingness to speak up and give suggestions, even in areas outside of their competence.

2.1.2 Method 635

If shyness is a problem, or there is a problem getting people together, this method is ideal. Once again, a problem is presented in sufficient detail to specify what needs to be addressed but without presenting or suggesting a solution. Each of six individuals writes down three ideas for solution of the problem, typically on a large sheet of paper or tablet. At a preselected time, these tablets are exchanged; each individual may now elaborate on the new ideas received or may generate three new ideas, or may simply relate the three original ideas (not preferred). Five exchanges take place such that no person gets back his/her original tablet, and each of the six tablets holds as many as 18 ideas for problem solution.

This method is useful in that it is very systematic and can generate a large number of solutions if each individual has a modicum of originality and can build on others' ideas. It has a drawback in that each person works in isolation, and thus, the group synergy is missing.

2.1.3 Delphi Method

This method is a polling process and can be valuable both in design processes and in situations where the future of a process is a subject of concern. The process typically consists of three steps. First, a series of suggested starting points for a design problem (or the future or a process) are generated by the process leader or by a panel of experts. These suggestions are regrouped and returned to the panelists, who are asked to add to the list. The resultant response list is then recollected and reordered, and the panel is asked to evaluate and comment on the reordered and expanded list.

An example of the use of this method might be to predict the future of the process of giving anesthesia during major surgery. Your preliminary letter to the chairs of anesthesiology at major medical centers might request a simple listing of key events in place now and some suggested future modifications of these processes. Your next letter would summarize the several responses that you obtained and might ask for both a timetable and a list of additional comments. Your third round would ask for advice on the practicality of each of the predictions and the necessity for related events to occur to make an event happen.

This method relies on the willingness of experts to respond to a questionnaire in a timely fashion. With most surveys running at a maximum of 30% return, you will need strongly motivated individuals on your panel. (Remuneration is often used to up the response rate.)

2.1.4 Synectics

Synectics is a term that describes a way of looking at analogies of terms relating to a problem as described. The process, briefly described, involves the following steps: First, the problem to be solved is presented to a small group. The group discusses the problem and the environment of the problem to the point that they are familiar with the problem and are able to articulate it. They then operate by looking at analogies and forcing relationships (embracing the irrelevant).

An example of the use of this methodology might be looking at ways to close a defect in the heart, for example, in the case of atrial septal defect. The problem is that there is a hole in the heart between the two atria; this hole needs to be closed by something that is small when introduced into the patient but large enough to cover and close the hole when deployed or opened. The key to this problem solution is to look at the key words in the last sentence: cover, close, open, small, and large. These key terms should enable you to make a number of analogies regarding devices that do one or more of these things; the most obvious would be to make the analogy to an umbrella (which, as it turns out, is a "solution"). Another could be to compare this with patching a tire on your car; thus, a patch would be needed.

There are variations on this theme that can be used, such as randomly picking words from a dictionary and trying to apply them to the problem solution (forcing a fit). This method is somewhat better than brainstorming, if the problem to be solved has an analogy and your group is willing to explore seemingly bizarre trains of thought.

2.1.5 Other Methods

One interesting variation on brainstorming is a fairly structured approach proposed by Dr. Edward de Bono that utilizes "six thinking caps." During a meeting on problem solving, the facilitator (blue hat) guides the conversations of others who wear white hats while gathering information, red hats while expressing emotions, black hats while expressing caution, yellow hats while being enthusiastic, or green hats while being creative. The objective of the hats is to allow persons to express feelings representative of the hats exclusively, rather than a combination of unstructured feelings as might be the case in a brainstorming situation. Changing hats allows one to "change gears" without "exposing" oneself.

2.2 CONVENTIONAL SOLUTION SEARCHES

Most of the previous section discussed techniques that required the use of other live humans to begin a solution search. A far more vast supply of information exists in web-based and print literature, especially patent databases. Bluntly put, most solutions that are generated (senior design projects or industry projects) involve use of solutions already demonstrated in the literature.

2.2.1 Web-Based and Print Literature

For students, a visit to (or from) a librarian at your university specializing in the engineering and sciences literature is a valuable first step. Most libraries subscribe to specialized databases that are not otherwise accessible (from your home or in the public libraries). Most major publishers (IEEE, Elsevier, CRC Press, etc.) offer packaged electronic access to sections of their literature (for fees that your local library cannot afford). An hour or so lecture/demo session from your librarian will be time well spent, especially if the proper use of Boolean search terms is covered!

Google Scholar is preferred over Ask, Google, and so forth.

For most projects, a search of the information contained in the US Patent and Trademark site (www.uspto.gov) is mandatory. (For some grading schemes for senior design projects, this search is mandatory! For most industrial projects, this is not only mandatory but also necessary to avoid lawsuits for patent infringement! For example, the $1 billion Apple vs. Samsung suit, 2012.) A simple patent text search allows the use of one or two terms in various parts or the entirety of a patent. Use of the search term *embolus* (for example, in all fields) searched for in the title of granted patents in the time period of 1996–2012 yielded 7337 "hits" in the database. The site also lists many other international patent database sites, such as the Japanese patent site, some of which allow for similar patent key word searches.

Many print trade magazines exist for product design, and several are specific for medical product design. Some magazines (*Medical Design Online* and *Medical Industry Today*, for example) send daily e-mails regarding work in the field; several maintain websites that allow search functions for devices and products.

A partial listing of the magazines received includes the following:

Medical Edge
Product Design and Development
Biotechniques
Medical E-News Daily
Desktop Engineering
R & D
Bioscience Technology
Surgical Products
Drug Discovery and Development
Device Daily Bulletin (FDA News)

All are useful for keeping track of new developments, market trends, and so forth. The latter is most useful for up-to-date news regarding device recalls, new approvals, and so forth.

2.2.2 Solutions in Nature and Analogies

Many design problems may have been solved in nature and may be transferred to design problems at hand. For example, the motion and flexibility of a worm should be studied if one is to look at improved catheter designs. The Eiffel Tower design was said to be mimicry of how bones support weight. A web search on Amazon.com for just the term *biomimetics* will yield over 200 book "hits" (2012). The website www.nature.com/nature has a search function that allows a search on such terms as *biomimicry*. One article, "Life's Lessons in Design," is a standout example of design and biomimicry. Another titled "AutoNAD—Nature Inspired Design" refers one to the site http://www.asknature.org/, which is replete with examples of biodesigns (1500 and climbing) that may be of value in your work.

Biomimetics involves the application of "nature's solutions" to the problem at hand. Examples of biomimetics include the use of sonar (mimicking bat calls) and Velcro (mimicking sticktights or cockleburs). Protective coloration/recoloring may have inspired camouflage suits. Spiderwebs are analogs for fishing nets. Firefly flashes have inspired detection of bacteria and tracking of nerve impulses. Geckos have inspired adhesives and climbing robots.

A final note or two: The use of biomimicry may be a top-down or bottom-up process. A bottom-up process would involve studying a particular bioprocess (or solutions) and trying to figure out how to create a useful tool for sale. An example of a bottom-up process might be, for example, studying the self-cleaning properties of the lotus leaf and generating a self-cleaning coating for windshields. A top-down process normally involves a solution search for a particular problem, for example,

improved suture materials; this might thus inspire a study of the tendrils of moonflowers and grapes. You might consider involving a biologist in your design team!

2.3 FUNCTION ANALYSIS

Many design problems will involve the use of flowcharting tools to assist in understanding the processes under study in order to improve or modify them. Properly done, these flowcharts will assist in the analysis of delays, patient irritations, added costs, and the like. Several levels of analyses may be of use, from simple process charts to fairly complicated combinations of signal, material, and information flows. Overall, the process of flowcharting can be an excellent communication tool and can give insight into problems with a process.

2.3.1 Simple Process Charts

Process charts can be extremely simplistic and tell an unequivocal story. Figure 2.2 details the process of applying a Band-Aid; one can almost imagine going through the process oneself while reading through the description. The shapes used in the diagram are fairly common, with many flowcharting systems typically using circles or ellipses for processes, arrows for designation of transport, diamonds for storage, squares for inspections, and *D*s for delays or wait states. The example that follows is an extremely short diagram but is illustrative of ways to display these data and potentially to make use of them. An extensive diagramming of a system could allow one to ask the following questions: Where can I get rid of delays? How is the transport of several parts to be facilitated to speed up this operation? How many operations are my workers being asked to do per

Date: August 8, 2007 Location: Office
Analyst: King Process: Apply Band-Aid

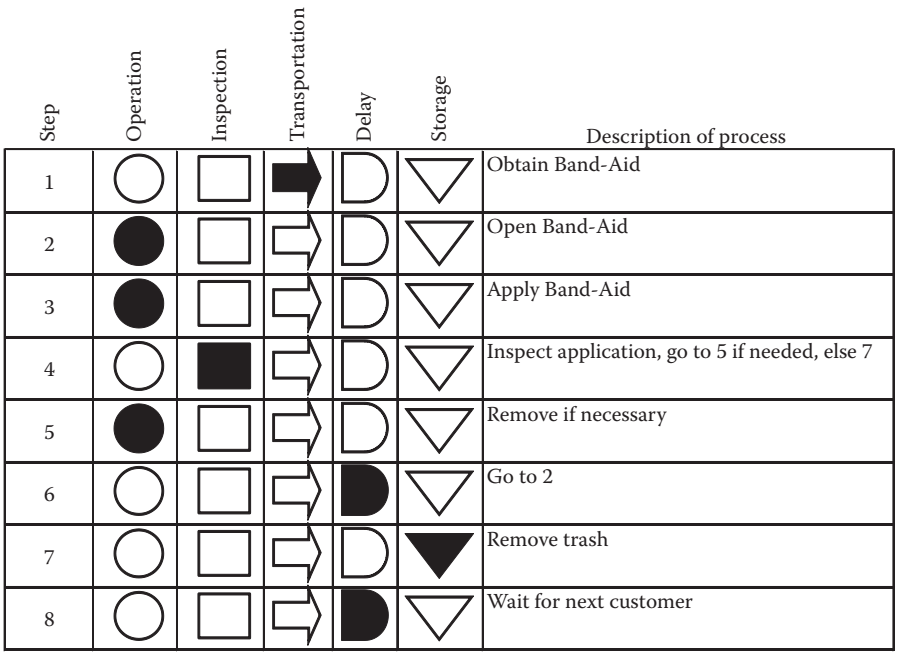


FIGURE 2.2 Process diagram for applying a Band-Aid.

minute? Why am I seeing carpal tunnel syndrome? Expansion of this diagram, with addenda on each line indicating distance traveled during an operation, for example, may facilitate studies for the improvement of the entire process (minimize distance traveled, minimize delays, etc.). Most flowcharting programs will additionally have the ability to annotate, with arrows, decision points that allow for retracing of steps backward if, for instance, there is a failed inspection.

2.3.2 Clinic Flowcharts

Figure 2.3 represents the path of a patient in a hypertension clinic. The rectangles represent operations such as sign-in and physician interaction. The large *D*s represent delays in the system. Note the nature of the path through the clinic and the emphasis on delays. This figure emphasizes the fact that this system is linear, that each event must be completed prior to the next beginning. From a patient point of view, this can be extremely frustrating, as the delay times accumulate. Overall waiting time (delay) for a patient is from 12 to 70 min for this process, which involves only 8 min of interaction with professionals, 5 min of that with the physician. As the physician is the only one in charge of emptying rooms, he/she can be blamed for this waste of time. A wait time of over 60 min (once!) for the first room caused one of the authors to switch physicians and clinics!

2.3.3 Flowcharts with Decision Points

To speed up a clinic process, at least for some patients, ancillary personnel can be used in the patient care-taking and advising process. Figure 2.4 demonstrates a modification of the previous flowchart wherein a nurse or other medical practitioner can take the weight, pulse rate, medication listing, and blood pressure data (if needed) and screen the patient to see if the patient needs to see the physician or can be seen by an RN or other health care worker for any update on medications or other matters. The diamond in the flowchart is a decision point; the branches signify a *yes* or *no* branch condition.

This revision of the hypertension clinic allows three branching points, which, on average, will allow for faster patient clinic visits by decreasing wait times via the use of ancillary personnel. Overall wait time has been reduced from 22–70 min to 5–20 min for the MD path, 5–10 min for the RN path, and zero for the ancillary personnel path in this model. The physician time is utilized for "needy patients" rather than the entire clinic's scheduled patient load. This can lead to improved clinic utilization if planned wisely, as many patients will be status quo and will not need a physician interaction. This model is analogous to well-run dentist offices where dental hygienists take care of the majority of patients' minor needs while the dentist takes care of the remainder.

What has been presented is some very rudimentary flowcharting information, the minimum necessary to understand some of the essentials needed for a starting analysis of clinic and other process analysis as a prelude to redesign of the process. Many other variations and embellishments

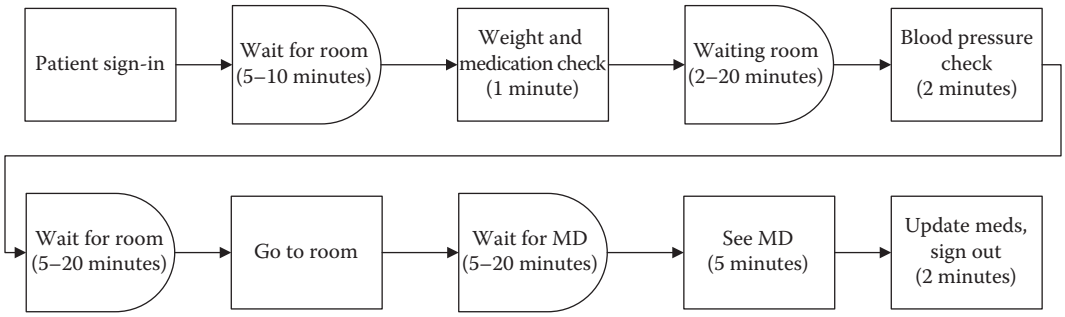


FIGURE 2.3 Blood pressure (hypertension) clinic flowchart. Numbers indicate length of delay or interaction time in minutes.

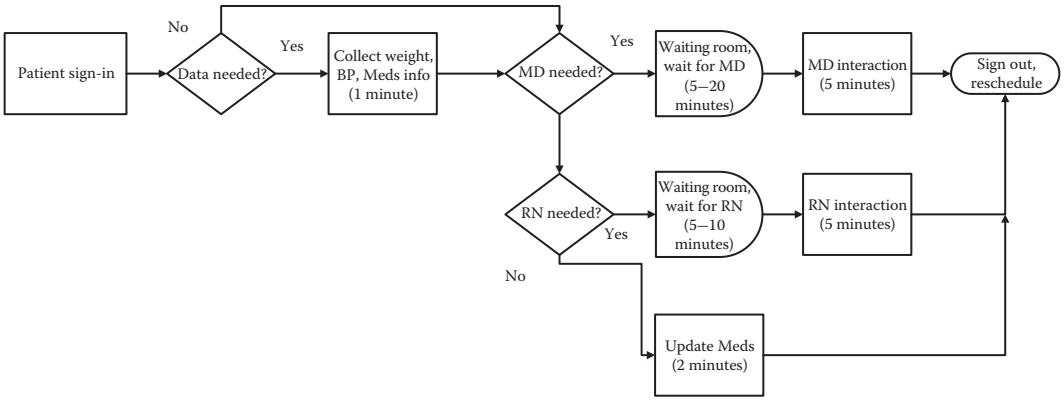


FIGURE 2.4 A faster hypertension clinic flowchart.

on the previous material are part of normal flowcharting programs, such as the use of color to identify particular paths; the use of additional annotation to indicate complaints about sections of the process; and the use of additional symbols specific to a number of other processes, such as design of databases, process diagrams for the food industry, and so forth. Some common variations for systems involving electromechanical devices involve the simultaneous overlay of material flows, information flows, and energy flows. Many commercial products have a wide variety of template patterns available for use. Two of the more commonly used commercial packages are Microsoft's Visio and Micrografx FlowCharter; a few other programs are available on the web for free, but most have a limited time trial associated with them. Software packages exist that emulate processes such as patient clinic visits such that variables, for instance, the effect of the number of examination rooms or number of clinic staff, may be varied and the effect of this on patient throughput estimated (High Performance Systems program Stella, for example).

2.4 ELEMENTARY DECISION-MAKING TECHNIQUES

In Chapter 4, the need to define well the parameters involved in the design problem statement will be very strongly emphasized. Terms such as *demand* and *wish* will be a part of the design analysis when design choices are being considered. Alternate terms involve objectives, quality, and function. The purpose of this section is to introduce some elementary concepts in the decision-making processes that may be selected in a solution search.

2.4.1 Selection Chart

A selection chart that might be used in a design process is shown schematically in Table 2.1. The essence of the design chart is that design demands are listed vertically and concepts or design choices being considered to perform these demands are listed horizontally. If a choice will not work, a "–" is entered in the intersection; if the opposite, a "+" is used. If a design choice is uncertain, a "?" symbol is employed. The final scoring with this simplistic chart simply asks the following question—does this column (choice) meet all criteria? If not, the design choice is rejected. If there are only "+" and "?" symbols, the particular choice will need to be investigated further.

As an example, consider the design decision for a proper writing implement for a grade school class in a damp environment. Table 2.2 might be an example of a product selection matrix. This example is simplistic and is meant only as an example. The process can work very nicely if there are few choices and most are go–no go in nature. A drawback is that there are no "shades of gray" or partial solutions allowed, and, as will be seen in a later discussion on invention, conflicts yield only dismissal of the choice, rather than resolution of the conflict via an inventive problem solution.

TABLE 2.1
A Simplified Design Selection Process Diagram

	Choice Number			
Demand #	**1**	**2**	**3**	**4**
1	+	+	?	+
2	+	–	–	+
3	+	+	–	?
Summary	Go	No go	No go	Recheck

TABLE 2.2
An Example of a Product Selection Matrix

	Choice			
Demand #	**Fountain Pen**	**Pencil**	**Chalk**	**Marker**
1. Writes on paper	+	+	?	+
2. Won't stain hands	–	+	+	–
3. Damp paper tolerant	?	+	?	?
Summary	No go	Go	Recheck	No go

2.4.2 Evaluation Charts

The next level up in complexity to the previous selection chart is an evaluation chart. This chart generally is used to assist in the ranking of various wishes, qualities, or other aspects of a proposed solution. Wishes or qualities are tabulated in a vertical column; each of these are assigned weights (importance) on an arbitrary scale, often ranging from 1 to 10, for example. No zero values are assigned as this would dismiss this row as a valid choice. Each set of columns from this point on carries the value of the particular column's solution, the net weight of the product of the solution, and the weighting given to that wish. The totals are then added for each proposed solution, and the "winner" is normally the column with the highest total. A fabricated example for a Daddy Warbucks's transportation choices between New York City and Rome for vacation purposes is given in Table 2.3.

In this example, the maximum possible score for a mode of transportation would be 100 (the total of the weights times the maximum weight of 5 each); thus, the choice of an ocean liner meets 87% of the person's wishes, versus the 59% figure for the commercial airliner. This method is subjective but is useful to help rank order a potentially large list of choices and wishes.

TABLE 2.3
Transportation Evaluation Chart, Maximum Weight = 5

		Commercial Airline		Ocean Liner	
"Wish"	**Weight**	**Value**	**Product**	**Value**	**Product**
High speed	3	5	15	2	6
Convenience	5	4	20	5	25
Comfort	5	3	15	5	25
Low cost	2	2	4	3	6
Food and drink	5	1	5	5	25
Total			59		87

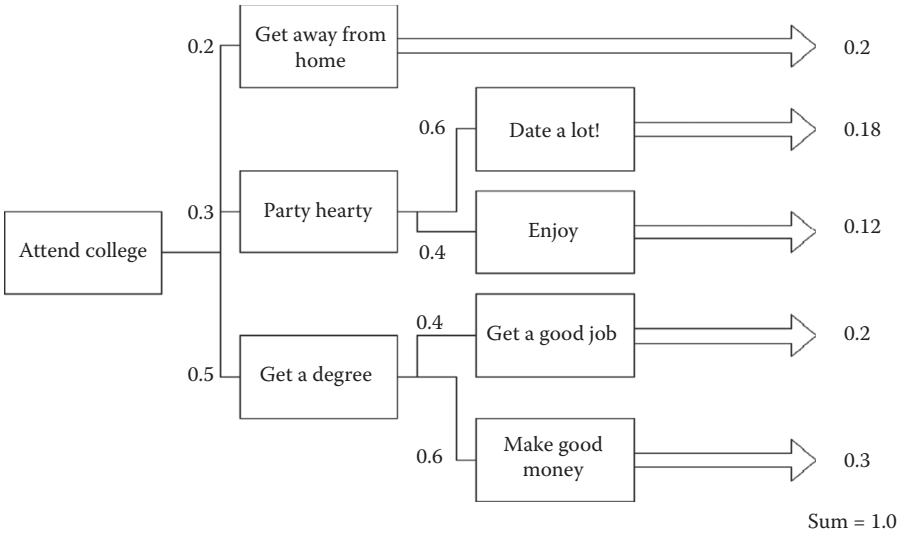


FIGURE 2.5 Objectives tree for the process of attending college.

2.5 OBJECTIVES TREES

The final minor evaluation process involves the generation of an objectives tree. This is a formulation that involves the assignment of priorities to a series of objectives and subobjectives such that a determination of the value of each of several subobjectives is quantified in the designer's mind. At the first branching, each subobjective is given a weight such that the sum of all weights is 1. At every successive branching the weights continue to sum to unity, but the overall weight of each branch is the product of all branchings prior. An example objectives tree to illustrate this process is given in Figure 2.5.

The objectives tree that follows is meant to be simple but illustrative. In actual practice, the tree may have many more branchings and levels of branching. The overall value of such diagrams is that they may give insight into overall priorities in a complicated situation. The drawback is that such trees are based upon the designer's personal bias as to the value of each branch, which will be borne out by the values in the final column.

2.6 INTRODUCTION TO QUALITY FUNCTION DEPLOYMENT DIAGRAMS

The process known as quality function deployment (QFD) is a structured approach to assist in translating customer requirements into realistic goals and sometimes even manufacturing specifications, dependent on the level and complexity of the structures used. This section will give an overview of only the first level of the QFD process, that of building most of the first and most valuable diagram, which is intended to relate the qualities that a customer wants to the functions that the device or process must perform. The deployment part of the process involves (generally) the manufacturing or other specification processes; this will be left for a later discussion. The first process is, in fact, an extension of some of the material previously covered. A sample diagram for the process of evaluating a marriage partner will be used to introduce the topic (see Figure 2.6).

The QFD diagram that follows is similar to ones that would normally be used in product comparison and product planning exercises. The function of the device is normally plotted on the vertical axis of a grid that is used for the comparison of "your product" and the competitors. In this case, we might posit that the function of marriage is to enable a couple to have legally recognized sex, reproduction, and companionship. The qualities desired in this partner as defined by your customers are elaborated on the

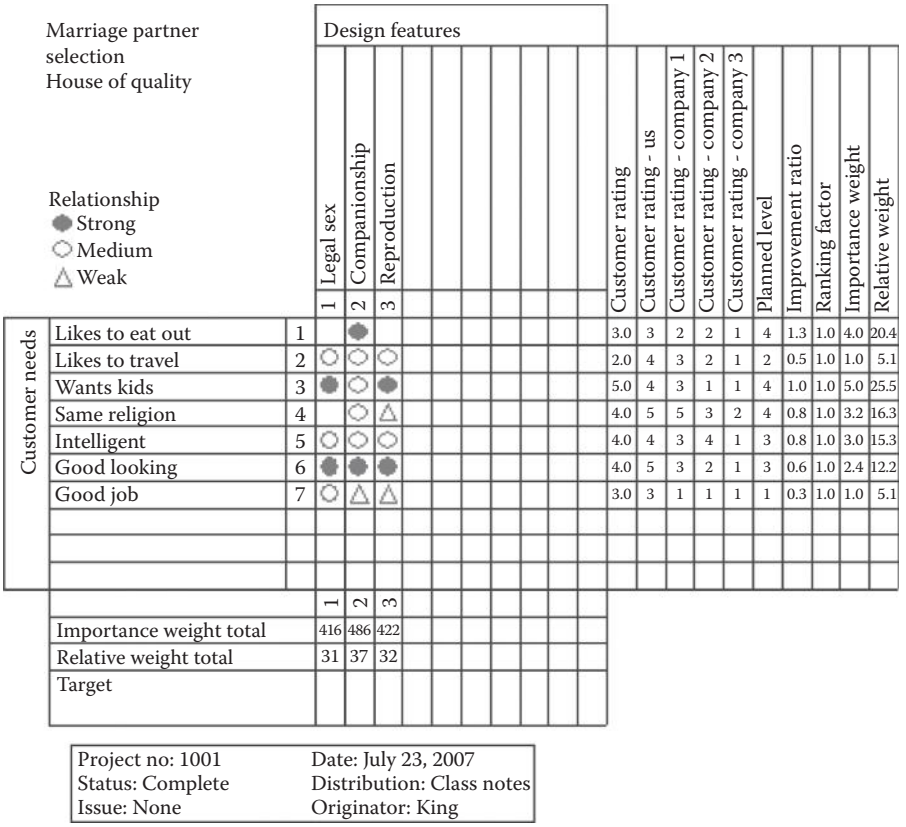


FIGURE 2.6 QFD diagram for the process of marriage partner selection.

left-hand axis. The relationship between qualities and functions is designated with a symbol, such as a filled-in circle if they are highly correlated, an open circle if slightly so, a triangle if minimally so, and so forth ("likes to eat out" correlates well with "companionship," for example). This ranking of functions (dependent on the software used) then allows a comparison of the relative importance of each of the functions (so that companionship is most highly desired in this example). The right-hand side of the figure allows for entry of customer importance of each item (rating), the customer rating of our product ("us") versus three competitors, a goal level (planned), a ranking factor for each of the planned levels, an improvement factor desired (planned over desired), a ranking factor for each of the improvements, and a calculation of relative weight (importance) of each of the "improvements." One can now use this diagram to "select" a best partner, based, for example, on calculations involving the summed product of customer rating times customer rating of "us" versus the three listed competitors. Alternately, a best "improvement" over "us" could be selected based upon the relative weights of improvements (final column) and the customer ratings relative to planned levels.

On occasion, the interactions between the functions are also plotted, using a triangular matrix attached to the top of the function columns. These interactions may also lead to design considerations that may need to be resolved, as there might be a conflict between two of the variables listed. This triangular matrix, when added to the previous diagram, gives rise to the name "House of Quality" that is often attached to such a display. These negative interactions may be resolved using other techniques, such as "inventive problem solving," to be discussed next.

Software to generate QFD diagrams is offered for free and for cost on various websites. For minor problems, some users simply modify an Excel spreadsheet to capture the needed titles and rankings and calculate the comparisons; most commercial packages are improvements on this basic method.

Please note that the rankings involved are "the voice of the customer" and may not yield the best outcome for your design process, as the rankings involve perceived qualities needed and not "facts."

The previous discussion of QFD is only introductory as it includes only the first level of a full QFD process. The full process involves two more levels of detail and may be used in planning for production of devices and processes. This will be discussed further in Chapter 4.

2.7 INTRODUCTION TO TRIZ

It was mentioned earlier that the patent database is a site for initial idea solution searches using key word searches. An alternate method would be to look for distillations of patent materials in terms of methods for solving design problems. Such a method was developed initially in the late 1940s by Genrich Altshuller in the Union of Soviet Socialist Republics; this method has been continually upgraded and added to in the intervening years. Altshuller held the position of patent clerk in the Russian Navy patent office; his work allowed him to study and distil design solution methodologies from inspection of thousands of patents. His work formed the basis for a series of papers on the theory of inventive problem solving; the Russian acronym for this is TRIZ.

Altshuller's goals were to codify what knowledge he could from the patent database and reduce the design process as much as possible to a step-by-step procedure. Some of his accomplishments are briefly listed as follows:

1. Altshuller recognized that problem solving ranged from the application of methodology that is commonly used in whatever specialty one is working in to true discovery entailing the development of new science or discovery of new principals. As the level of difficulty increased, the number of solutions to be examined increased. Highly difficult problems generally involved the use of material outside of one's own specialty.
2. He recognized that most inventions went through different stages of development with a finite number of variations on different themes of transition. One such theme is that systems tend toward increasing ideality, another that systems tend toward microsystems, and another that systems tend to need less human involvement.
3. Altshuller's first major observation was that most inventive problems involved a solution of technical contradictions (negative interaction between desired functions or between desired qualities). This work gave rise to two useful devices, an inventive principles listing (also known as engineering parameters) and a technical contradiction matrix. The principles list (Appendix 3) includes 40 different parameters that can be applied in the design of a system. This initial listing includes such terms as *segmentation*, *asymmetry*, *extraction*, *nesting*, and so forth. The technical contradiction matrix is a 39×39 matrix of contradictions (Appendix 3); one axis lists all features that conceivably could be changed in a system (such as the weight of a moving object), and the other axis repeats this list but is now labeled "undesired result." The intersection of two features lists suggested solutions from the principles list. An example intersection point is the weight of a moving object (say an airplane wing, row 1), where increasing weight compromises strength (column 14); one solution technique is to use composites (solution 40), which is, in fact, in practice.
4. Altshuller went well beyond this level of work, studying and developing advanced inventive problem solving techniques that are more algorithmic in nature. Object–action diagramming techniques and directed product evolution arose from this work. These subjects will be included later as specific topics in Chapter 6.

2.8 EXTENDED TRIZ DESIGN TECHNIQUES

The initial part of the design/specify/build/test procedure is the most demanding; if the initial conception of the problem and the consequent design solution is inadequate, the product or solution

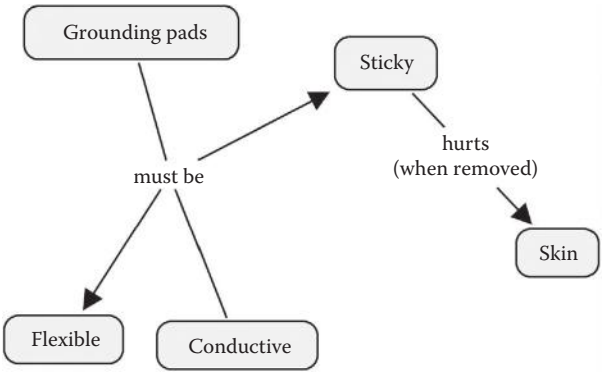


FIGURE 2.7 Concept map for grounding pad needs and problems.

may be doomed to failure. This chapter covered some of the fundamental design tools used in initial attempts at a design solution; this section is meant to give an overview of another method. This section will include a partial example problem "ideation" using a software package called "Innovation Workbench," a software package that is an outgrowth of the basic TRIZ method discussed in this chapter. It has some properties in common with another package, TechOptimizer, which also evolved from the same roots.

One example to be discussed is fairly straightforward; it is a problem that occurs daily in our hospital environment at this time. When electrosurgical units are used to cut or cauterize, for example, during the excision of a skin cancer, a need exists for a form-fitting (flexible) grounding pad to ensure that the majority of return current flow is though the grounding pad, rather than through some other small part of the body, such as a finger, that might otherwise offer a return path for the current. This smallness implies a potentially high current density and concurrent burn injury potential. After the surgery is completed, a second potential exists for injury—when the pad is removed, there exists the potential for skin abrasions and tearing due to the "stickiness" of the pad, which obviously is what kept it on to begin with. This injury potential is more likely with elderly patients, due to the decreased elasticity of their skin. A concept map for this problem statement may be seen in Table 2.3 and Figures 2.5 through 2.7.

2.8.1 The Use of Innovation Workbench

Innovation Workbench is a software package that guides a designer through the initial design/solution search process by having the designer fill out material in a questionnaire. The questionnaire consists of five main parts. The first part is termed "Innovation Situation Questionnaire"; this section consists of nine main sections that serve to document the current situation and the allowable changes that the designer might be able to make. The second section, "Problem Formulation," requires that the designer build a diagram that interrelates the elements of the process/system under study, with an emphasis on the generation of "good" interactions versus "detrimental" interactions (in the chart to follow, arrows to a sharp corner rectangle vs. arrows to a rounded corner rectangle). This diagram is termed a *conflict diagram*. The detrimental interactions are analogous to the technical contradictions discussed in the section on TRIZ in this chapter, harmful effects in concept diagrams, and negative interactions between functions in QFD diagrams. The good and bad interactions in the conflict diagram are used to generate directions for innovation, some of which are then selected for further study in a section titled "Prioritize Directions." Finally, two sections are devoted to the "Development of Concepts" and "Evaluation of the Results"; these sections will receive little

development here, as the majority of the useful part of this exercise is developed in the first three sections.

In Section 7.9.2, the program headers and all numbered lines are from the program itself; the other lines and diagram are input by the user of the program. The initial sections with the "≫" delineation are the program-derived suggestions based upon the user–input conflict diagram for the problem. The example is the aforementioned grounding problem.

2.8.2 Ideation Process

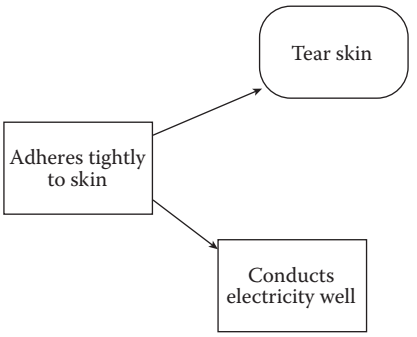
Ideation Process

Innovation Situation Questionnaire

1. Brief description of the problem
   See PowerPoint, grounding pad injury, or material in this text.
2. Information about the system
   2.1 System name
   Grounding Pad.
   2.2 System structure
   The grounding pad is placed on the subject's body in a manner so as to allow current to flow in a circuit.
   2.3 Functioning of the system
   The primarily useful function is the removal, through the pad, of electric current.
   2.4 System environment
   Typical situation—surgery.
3. Information about the problem situation
   3.1 Problem that should be resolved
   Removal without compromise of the patient's body.
   3.2 Mechanism causing the problem
   The adhesion of the pad to the skin pulls the skin during removal.
   3.3 Undesired consequences of unresolved problem
   Skin gets injured, sometimes torn.
   3.4 History of the problem
   I guess a long time, need to review the literature.
   3.5 Other systems in which a similar problem exists
   I guess the acne/blackhead strips...
   3.6 Other problems to be solved
   None at this time.
4. Ideal vision of solution
   A grounding pad is designed that adheres well when needed and then can be easily removed.
5. Available resources
   Hospital BioEngineering (BE) team, MD help, etc.
6. Allowable changes to the system
   Some leeway on cost, probably can change materials, etc.
7. Criteria for selecting solution concepts
   Easy removal with safe use.
8. Company business environment
   BioMedical Engineering (BME) senior design.
9. Project data
   Gant chart, timelines, team, etc.

Problem Formulation

1. Build the diagram



2. Directions for innovation
   10/9/2003 9:51:20 AM Diagram 1
   a. Find an alternative way to obtain [the] (conducts electricity well) that does not require [the] (adheres tightly to skin).
   b. Consider transitioning to the next generation of the system that will provide [the] (conducts electricity well) in a more effective way and/or will be free of existing problems.
   c. Find an alternative way to obtain [the] (adheres tightly to skin) that offers the following: provides or enhances [the] (conducts electricity well), does not cause [the] (tears skin).
   d. Try to resolve the following contradiction: the useful factor [the] (adheres tightly to skin) should be in place in order to provide or enhance [the] (conducts electricity well), and should not exist in order to avoid [the] (tears skin).
   e. Find a way to eliminate, reduce, or prevent [the] (tears skin) under the conditions of [the] (adheres tightly to skin).

Prioritize Directions

1. Directions selected for further consideration
   a. Find an alternative way to obtain [the] (conducts electricity well) that does not require [the] (adheres tightly to skin).
      i. Improve the useful factor (conducts electricity well).
      ii. Obtain the useful result without the use of [the] (conducts electricity well).
      iii. Increase effectiveness of the useful action of [the] (conducts electricity well).
      iv. Synthesize the new system to provide [the] (conducts electricity well).
      v. Apply universal operators to provide the useful factor (conducts electricity well).
      vi. Consider resources to provide the useful factor (conducts electricity well).
   b. Consider transitioning to the next generation of the system that will provide [the] (conducts electricity well) in a more effective way and/or will be free of existing problems.
      i. Improve ideality of your system that provides [the] (conducts electricity well).
      ii. Consider the possibility of transforming the existing system that provides [the] (conducts electricity well) into a bisystem or polysystem.
      iii. Consider segmentation of the existing system that provides [the] (conducts electricity well).
      iv. Consider restructuring the existing system that provides [the] (conducts electricity well).
      v. Increase dynamism of the existing system that provides [the] (conducts electricity well).
      vi. Increase controllability of the existing system that provides [the] (conducts electricity well).

vii. Make the existing system that provides [the] (conducts electricity well) and/or its elements more universal.

c. Find an alternative way to obtain [the] (adheres tightly to skin) that offers the following: provides or enhances [the] (conducts electricity well), does not cause [the] (tears skin).
   i. Improve the useful factor (adheres tightly to skin).
   ii. Obtain the useful result without the use of [the] (adheres tightly to skin).
   iii. Increase effectiveness of the useful action of [the] (adheres tightly to skin).
   iv. Synthesize the new system to provide [the] (adheres tightly to skin).
   v. Apply universal Operators to provide the useful factor (adheres tightly to skin).
   vi. Consider resources to provide the useful factor (adheres tightly to skin).

d. Try to resolve the following contradiction: the useful factor [the] (adheres tightly to skin) should be in place in order to provide or enhance [the] (conducts electricity well), and should not exist in order to avoid [the] (tears skin).
   i. Apply separation principles to satisfy contradictory requirements related to [the] (adheres tightly to skin).
   ii. Apply 40 innovation principles to resolve contradiction between useful purpose of (adheres tightly to skin) and its harmful result.

e. Find a way to eliminate, reduce, or prevent [the] (tears skin) under the conditions of [the] (adheres tightly to skin).
   i. Isolate the system or its part from the harmful effect of [the] (tears skin).
   ii. Counteract the harmful effect of [the] (tears skin).
   iii. Impact on the harmful action of [the] (tears skin).
   iv. Reduce sensitivity of the system or its part to the harmful effect of [the] (tears skin).
   v. Eliminate the cause of the undesired action of [the] (tears skin).
   vi. Reduce the harmful results produced by [the] (tears skin).
   vii. Apply universal Operators to reduce the undesired factor (tears skin).
   viii. Consider resources to reduce the undesired factor (tears skin).
   ix. Try to benefit from the undesired factor (Tears skin).

2. List and categorize all preliminary ideas
   From the previous list, read each item and place here.

Develop Concepts

1. Combine ideas into concepts
2. Apply lines of evolution to further improve concepts

Evaluate Results

1. Meet criteria for evaluating concepts
2. Reveal and prevent potential failures
3. Plan the implementation

2.8.3 Summary

The fairly extensive material in the previous several pages should leave one at least the impression that the overall process can be all-encompassing. The crux of a good solution (and solution space) lies in the good development of the system diagram; if the diagram properly captures all the relevant interactions and conflicts in a system design, the (patented) solution generation algorithm should generate a solution suggestion that will solve the design problem at hand. Other considerations that are forced by this program that are often overlooked are the requirement that one consider the environment (as this can often assist in problem solution.) At the very least, the use of such a program

provides a comprehensive structure for consideration of many design problems. Not shown here is the ability to reference patent databases and effects databases; the addition of these data makes this program a powerful tool.

2.9 CASE STUDY: CANCER CLINIC CHARTING

2.9.1 Background

Many hospital clinics service a mixture of well and ill patients. Such clinics are multiuse, serving as a screening clinic for the majority of the clients and as a triage and referral clinic for others. One such clinic that has been the subject of a design study is the Breast Diagnostic Center at Vanderbilt. The clinic patient pathway was in need of study to determine areas for improvement in services and in patient perceptions of the process.

2.9.2 Problem Statement

While charting the pathway of patients through a screening clinic (breast cancer screening) a means had to be found to display not only the process but also the patient perception of the process.

2.9.3 Problem Solution

The student involved in this process worked with her supervisor and the clinic staff to develop a bare-bones clinic flowchart for the process of breast cancer screening. A portion of the six-page flowchart may be seen in Figure 2.8.

Next, as several patients went through the clinic, the student accompanied them and additionally interviewed them as to their perceptions of the process. The patient concerns were overlaid on the clinic flowchart; the mood of the patients during the procedures was expressed in a thermometer form also on the chart. The overall combined process and patient perception flowchart is extremely informative, as a glance at Figure 2.8 for the section with a patient with diagnosed cancer will indicate (Figure 2.9).

The total chart was used to identify points of stress for patients during their clinic visit and was used in the redesign of the clinic operation and physical design of new space. (For other useful ways of envisioning information, the reader is referred to the texts by Edward R. Tufte.)

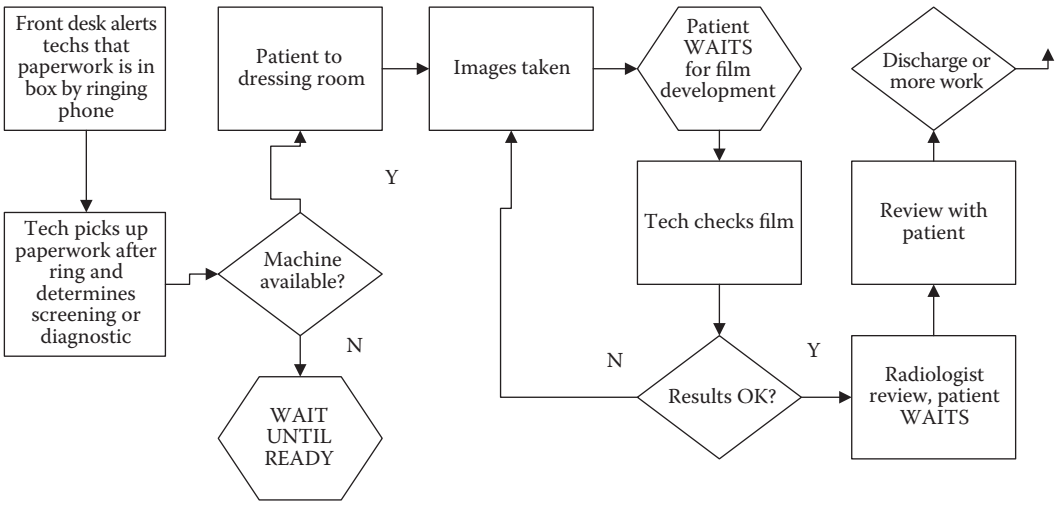


FIGURE 2.8 Partial section of the breast cancer clinic patient flowchart.

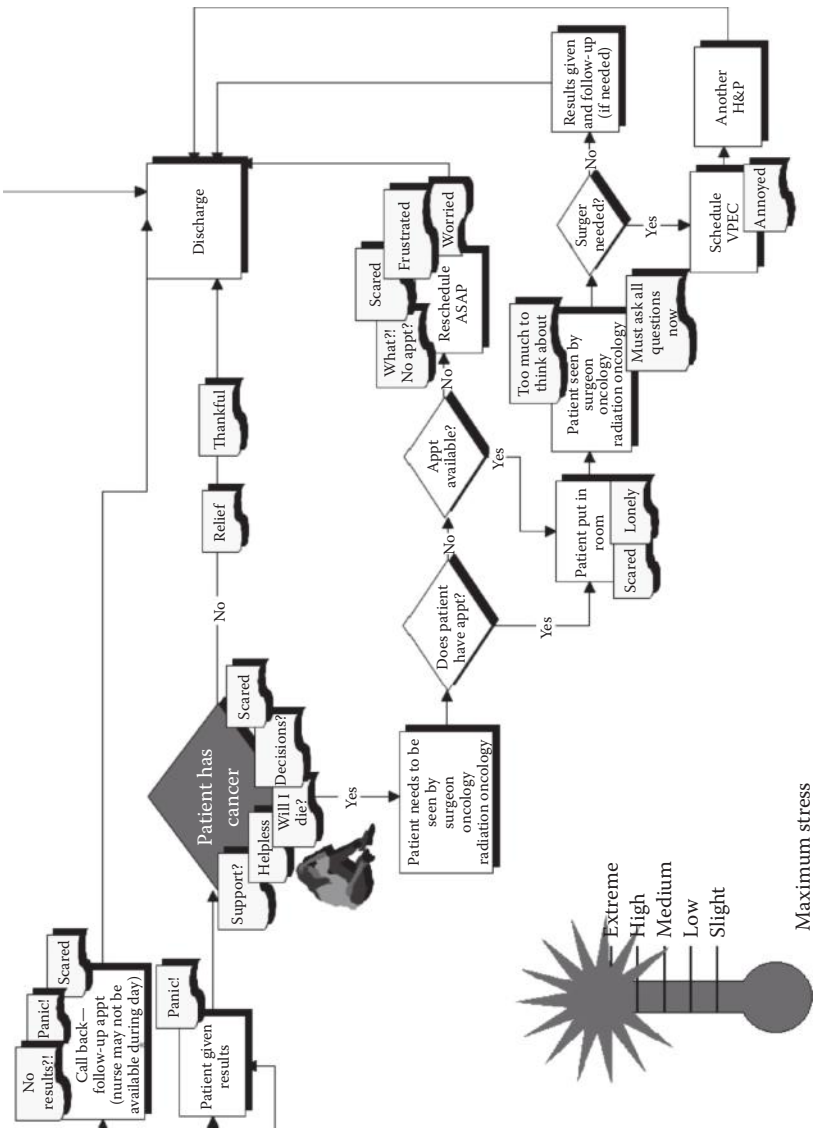


FIGURE 2.9 Cancer clinic diagnosis/discharge/follow-up section. VPEC, Vanderbilt Preoperative Evaluation Clinic; H&P, Health & Physical.

2.10 SUMMARY

This chapter introduced several simple design tools prior to an in-depth study of the overall process of design as applied to medical devices and processes. As such, it is generic in nature and may be applied to many design processes both in an engineering design environment as well as in personal decision making.

EXERCISES

1. Perform a web search with the search term "brainstorming." Evaluate several of the sites, try some of the software available, and report on the usefulness of the program.
2. Do a web search with the term "concept map." Find and explore one or more example concept maps.
3. Draw a process diagram for the process of taking hamburger meat, grinding it, and then flattening it and cutting out presized hamburger patties. The meat that is in between the patties is reinserted into the process just after the incoming meat is ground. What is wrong with this process? If necessary, do a web search to answer this question.
4. Visit the website www.jellybelly.com and find their process listing. Do a flowchart of this process, specifically identifying delays. Discuss means to speed up this process. Extra credit, request that samples be sent to your instructor.
5. Visit any website that has an example concept map that is of interest to you, print out the map, and comment on the value of it.
6. Pick two design terms or terms relating to a project you have worked on. Pick two different search engines and search on these two terms. What are the differences in yield? Would you recommend one search engine over the other? Why?
7. Do a web search on the term "biomimetics," find a good example of this as applied to a design problem, print it out, and discuss it.
8. Generate a simple process chart for the process of brushing teeth.
9. Generate a flowchart for the process of obtaining breakfast. Be sure to indicate delays and make suggestions to decrease same.
10. Generate a simple selection diagram to determine whom you will date for a formal dance.
11. Generate an evaluation chart to assist you in the determination between camping in the mountains and going to the beach for your vacation this year.
12. Generate a simple QFD chart for the selection of an automobile.
13. Generate a QFD diagram to help design a better device for closure of an atrial septal defect.
14. A problem that arose in the early use of long-barreled cannons was that they "wilted" during repeated use due to heating and uneven cooling, especially during rainstorms. Use brainstorming with one or two friends to help solve this problem. Reference the TRIZ contradiction matrix and attempt to find a solution. Document your choices.

SUGGESTED READING

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3 Design Team Management, Reporting, and Documentation

> Never tell people how to do things. Tell them what to do and they will surprise you with their ingenuity.
>
> **George S. Patton, Jr.**

Design management is a multistep process that is a necessary part of every product development process. Design management consists of the following:

- Design team construction and management
- Documentation techniques and requirements
- Reporting techniques

All form an integral part of success in developing a product. All are interrelated and interdependent. All will be audited by the Food and Drug Administration (FDA) and Quality System auditors if in industry. All are equally relevant to design in the university setting.

3.1 DESIGN TEAM CONSTRUCTION AND MANAGEMENT (INDUSTRY BASED)

The team is a basic unit of performance for most organizations. A team melds together the skills, experiences, and insights of several people. It is the natural complement to individual initiative and achievement because it engenders higher levels of commitment to common ends. Increasingly, management looks to teams throughout the organization to strengthen performance capabilities.

In any situation requiring the real-time combination of multiple skills, experiences, and judgments, a team inevitably gets better results than a collection of individuals operating within confined job roles and responsibilities. Teams are more flexible than larger organizational groupings because they can be more quickly assembled, deployed, refocused, and disbanded, usually in ways that enhance rather than disrupt more permanent structures and processes. Teams are more productive than groups that have no clear performance objective, because their members are committed to deliver tangible performance results. Teams invariably contribute significant achievements in all areas of a business.

A team is defined as an interdependent collection of individuals who work together toward a common goal and who share responsibility for specific outcomes of their organizations. The team is identified as such by those within and outside the team. A project team is a group of individuals whose members belong to different functions within an organization and are assigned to activities for the completion of a specific activity. Individual team members can be involved on either a part-time or a full-time basis. Their time commitment can change throughout the project depending on the stage of development. Project teams need to have the correct combination of skills, abilities, and personality types to achieve collaborative tension.

The purposes of the project team are as follows:

- Perform the research required to reduce risks and unknowns to a manageable level
- Develop and verify the user specification

- Prepare the project plan
- Design the project to match the specification
- Test the product to ensure all requirements are met
- Prepare the regulatory input
- Prepare the product for manufacturing
- Complete all required documentation
- Conduct a "lessons learned" review
- Update the lessons learned database

The approximate amount of time required of each participant as well as incremental expenses should also be estimated. Some examples of incremental expenses include model development, simulation software, travel for customer verification activities, laboratory supplies, market research, and project status reviews.

3.1.1 Definition of a Team

At the heart of a definition of *team* is the fundamental premise that teams and performance are inextricably connected. The truly committed team is the most productive performance unit that management has at its disposal, provided there are specific results for which the team is collectively responsible and provided the performance ethic of the company demands those results.

Within an organization, no single factor is more critical to the generation of effective teams than the clarity and consistency of the company's overall performance standards—or performance ethic. Companies with meaningful, strong performance standards encourage and support effective teams by helping them both tailor their own goals and understand how the achievement of those goals will contribute to the company's overall aspirations. A company's performance ethic provides essential direction and meaning to the team's efforts.

This crucial link between performance and teams is the most significant piece of wisdom learned from teams. It leads directly to the following definition: "A team is a small number of people with complementary skills that are committed to a common purpose, performance goals, and approach for which they hold themselves mutually accountable."

3.1.2 Characteristics of Teams

There are six basic characteristics of successful teams:

- Small number
- Complementary skills
- Common purpose
- Common set of specific performance goals
- Commonly agreed-upon working approach
- Mutual accountability

The majority of teams who are successful have their membership range from 2 to 25 people. The most successful have numbered approximately 12. A larger number of people can theoretically become a team, but they usually break into subteams rather than function as a single team. The main reason for this is that large numbers of people, by virtue of their size, have trouble interacting constructively as a group, much less agreeing on actionable specifics. Large groups also face logistical issues like finding enough physical space and time to meet together. They also confront more complex constraints like crowd or herd behaviors that prevent the intense sharing of viewpoints needed to build a team.

Teams must develop the right skills, that is, each of the complementary skills necessary to do the team's job. These team skill requirements fall into three categories:

- Technical or functional expertise
- Problem-solving and decision-making skills
- Interpersonal skills

A team cannot get started without some minimum complement of skills, especially technical and functional ones. No team can achieve its purpose without developing all the skill levels required. The challenge for any team is in striking the right balance of the full set of complementary skills needed to fulfill the team's purpose over time.

A team's purpose and performance goals go together. The team's near-term performance goals must always relate directly to its overall purpose. Otherwise, team members become confused, pull apart, and revert to mediocre performance behaviors. Successful teams have followed the following premises:

- A common, meaningful purpose sets the tone and aspiration.
- Specific performance goals are an integral part of the purpose.
- The combination of purpose and specific goals is essential to performance.

Teams also need to develop a common approach—that is, how they will work together to accomplish their purpose. Teams should invest just as much time and effort crafting their working approach as shaping their purpose. A team's approach must include both an economic and administrative aspect as well as a social aspect. To meet the economic and administrative challenge, every member of the team must do equivalent amounts of real work that goes beyond commenting, reviewing, and deciding.

Team members must agree on who will do particular jobs, how schedules will be set and adhered to, what skills need to be developed, how continuing membership is earned, and how the group will make and modify decisions, including when and how to modify its approach to getting the job done. Agreeing on the specifics of work and how it fits together to integrate individual skills and advance team performance lies at the heart of shaping a common approach. Effective teams always have team members who, over time, assume different important social as well as leadership roles such as challenging, interpreting, supporting, integrating, remembering, and summarizing. These roles help promote the mutual trust and constructive conflict necessary to the team's success.

No group ever becomes a team until it can hold itself accountable as a team. Like common purpose and approach, this is a stiff test. Team accountability is about the sincere promises team members make to themselves and others, promises that underpin two critical aspects of teams:

- Commitment
- Trust

By promising to hold themselves accountable to the team's goals, each member earns the right to express his/her own views about all aspects of the team's effort and to have his/her views receive a fair and constructive hearing. By following through on such a promise, the trust upon which any team must be built is preserved and extended.

3.1.3 Team Success Factors

There are six team success factors inherent to any effective team:

1. Multifunctional involvement
2. Simultaneous full-time involvement

3. Colocation
4. Communication
5. Shared resources
6. Outside involvement

Multifunctional involvement means representation at least of the following stakeholders:

- Customers
- Dealers
- Suppliers
- Marketers
- Lawyers
- Manufacturing personnel
- Service personnel
- Engineers
- Designers
- Managers
- Nonmanagers

All personnel should be involved with the team from its inception in person or, at the very least, via input via surveys.

Key team members—design, manufacturing, and marketing—must be represented *full time* from the start. The involvement of others should be full time for the duration of the most intense activity. Rewards should go to teams as a whole. Evaluation, even for members who are full time only for a short time, should be based principally on team performance.

Numerous studies indicate the astonishing exponential decrease in communication that ensues when thin walls or some distance exists between team members. For the most effective environment, team members must be in *close proximity.* (The best design teams on occasion are called "Skunk Works," based upon a famous design team working for Lockheed Martin.)

Communication is everyone's panacea for everything—but nowhere more so than in teams. Examination of successful teams has shown that the most important element in ensuring a team's effectiveness and success is the constant communication across functional boundaries. Regular meetings with all functional areas represented and written status reports circulated to everyone are the norm for effective teams.

Duplication of every resource for every development project is not always a true possibility. However, team research has reported that the sharing of resources between new product/service teams and mainline activities, including manufacturing, marketing, and sales, is a leading cause of delayed product development and introduction efforts. One option is to devote areas of laboratories or manufacturing areas *for the new product development* efforts.

Suppliers, distributors, and ultimate customers must become *partners* in the development process from the start. Much, if not most, innovation will come from these constituents, if the team trusts them and they trust the team.

3.1.4 The Team Leader

Successful team leaders instinctively know that their primary goal is team performance results instead of individual achievement, including their own. Unlike working groups, whose performance depends solely on optimizing individual contributions, real team performance requires impact beyond the sum of the individual parts. Hence, it requires a complementary mix of skills, a purpose that goes beyond individual tasks, goals that define joint work products, and an approach that blends individual skills into a unique collective skill, all of which produces strong mutual accountability.

Team leaders must act to clarify purpose and goals, build commitment and self-confidence, strengthen the team's collective skills and approach, remove externally imposed obstacles, and create opportunities for others. Most important, like all members of the team, team leaders do real work themselves. They also believe that they do not have all the answers—so they do not insist on providing them. They believe they do not need to make all key decisions—so they do not do so. They believe they cannot succeed without the combined contributions of all the other members of the team to a common end—so they avoid any action that might constrain inputs or intimidate anyone on the team.

Team leaders must work hard to do the seven things necessary to good team leadership:

1. Keep the purpose, goals, and approach relevant and meaningful.
2. Build commitment and confidence.
3. Strengthen the mix and level of skills.
4. Monitor timing and schedules for planned activities.
5. Manage relationships with outsiders, including removing obstacles.
6. Create opportunities for others.
7. Do real work.

A team leader critically influences whether a potential team will mature into a real team or even a high-performance team. Unless a leader believes in a team's purpose and the people on the team, they cannot be effective. In industry, a change in team leadership occurs when a review of team progress and current status does not meet expectations. Team progress and status is periodically reviewed by upper management, and changes are made if management thinks it is necessary. The departing leader may no longer work for the company, depending on the severity of the problem, or is placed on another team as a worker. When a leadership change is made, the new leader will be more forceful in his/her expectations of the team in order to bring the status of the work close to expectations. Longer work hours will be enforced to attempt to make up lost time, and subteam membership may be changed depending whether the new leader feels that the current membership is adequate. The new leader may appear dictatorial because of the pressure from upper management to meet new deadlines. The overall decorum of the team will be highly charged until the team is back on schedule.

3.1.5 The Design Team

The typical product design team is a collection of individuals from various departments within a company who come together for the specific purpose of designing and developing a new medical device. The design team is composed of two subteams:

- The core team
- The working team

3.1.5.1 The Core Product Team

The core product teams are responsible for performing the research required to reduce risks and unknowns to a manageable level, to develop the product specification, and to prepare the project plan. They are responsible for all administrative decisions for the project, regulatory and standards activity, as well as planning for manufacturing and marketing the device.

The core product team is composed of individuals representing the following functions:

- Marketing
- Engineering

- Electrical
- Mechanical
- Biomedical
- Chemical
- Software
- Reliability engineering
- Human factors
- Safety engineering
- Manufacturing
- Service
- Regulatory
- Quality assurance
- Finance

The leader of the core team is usually from engineering or marketing. The leader is responsible for conducting periodic team meetings, ensuring that minutes of such meetings are recorded and filed, establishing and tracking time schedules, tracking expenses and comparing them to budgeted amounts, presenting status reports to the senior staff, and ensuring that sufficient resources in all areas are supplied. The leader will also provide a performance evaluation of each member of the team to line managers.

The approximate amount of time required of each participant as well as incremental expenses, such as model development, simulation software, travel for customer verification activities, laboratory supplies, market research, and project status reviews, should also be estimated.

3.1.5.2 The Working Design Team

The members of the working team, primarily engineers, take the product specification and develop the more detailed design specification. Working teams exist in all areas of engineering, including electrical, mechanical, and software. Working team members are responsible for developing designs from the design specification, ensuring that all requirements are verified through testing, and providing test reports. Certain members may also be responsible for verifying requirements and validating the system as a whole. Individual working teams may be divided into subteams to address individual design assignments.

3.2 STUDENT DESIGN TEAM CONSTRUCTION AND MANAGEMENT

The prior section on design team construction and management represents an ideal that must be modified to be workable with student design teams. This section will elaborate on several of these differences.

3.2.1 Definition of a Student Team

The definition of a student team must again satisfy the description regarding accountability. The typical student team will need a mentor who is also accountable and willing to supervise a given project, donating an average of an hour or more per week to direct supervision of the design project. Additionally, an overall course supervisor should be available to intervene if necessary in the conduct of the design work, overall evaluation of a class, and coordination of judging exercises.

3.2.2 Characteristics of Student Teams

By definition, the six characteristics of successful teams will again apply. Teams should generally be of a small number; team limits of five per team are fairly common. The pressures due to the scheduling of meeting times for larger groups often prove to be insurmountable. For many biomedical

engineering problems, an interdisciplinary team (ME + EE + BME, for example, reflecting the needs of the project) is more likely to succeed at the development (at least) of a prototype than a single major group. For long-term projects, a mixture of upperclassmen and underclassmen (if possible) can provide continuity of effort. Interaction with and collaboration with nonengineering majors (such as marketing or management students) should be pursued if at all possible. The unique viewpoints these students might be able to add may be of value to your overall outcome and are potentially reflective of industry.

3.2.3 Team Success Factors

The six team factors for success apply directly to student design teams. Item six, "outside involvement," especially on the part of both the course instructor and the project mentor, is critical due to the general inexperience of the group with the (typical) material at hand. Communication must be positive; collocation should be strived for, at least for weekly planning/work delegation meetings. Overall effort levels should be approximately the same for each member, ranging from 2 to 3 hours per week per credit hour for the course.

3.2.4 The Team Leader

The initial choice of a team leader should be based upon having the requisite academic and social skill set to supervise a particular design project and team. Some design instructors will select the initial leader; others will allow the group to elect a member. With either method, the design group should not feel constrained to keep with a particular leader; the best leader may depend on the phase of the given project.

3.2.5 Special Considerations for Student Design Teams

Student design teams will often go through team developmental phases without realizing that the interrelationships between members and within the project are evolving. These phases may be summarized as follows:

- In phase 1, the group dynamic is one of "forming"; the group is setting its purpose, its structure, its membership, and individual "duties."
- There is almost universally a "phase 2" labeled "storming," in which conflicts arise regarding group purpose and individual expectations, leadership is called into question, the whole idea of doing a design project seems overwhelming, and so forth. This is a critical phase, which will be addressed again later in the chapter.
- Phase 3 is generally termed "norming," wherein management of relationships and tasks once again becomes normalized, and real work begins.
- Phase 4 is often called "performing"; tasks are completed, the project is evaluated, and there is a sense of completion of the project.
- On occasion, with the completion of a project, there is a sense of loss, occasionally termed "adjourning."

It is useful to question this listing, as not all groups go through all phases. Most groups will go through a period of crisis, where an internal or external assist may be needed.

Some of the options available to groups include the following:

1. Disband the group. If it is early enough, new projects may be found, and graduation requirements therefore may be met; otherwise, there is a major penalty.
2. Request intervention on the part of your advisor or instructor.

3. Try to talk it out in a nonconfrontational manner.
4. Use peer evaluation tools to provide feedback, both positive and negative, to each of your team members.
5. Check with your instructor to see if there is a mechanism in place to give different grades to different students, based upon peer evaluation as well as instructor and supervisor grading. If there is, be sure to understand the ground rules, and be sure all team members agree to abide by these rules.
6. Do nothing.
7. Reorganize.

Items 3 and 4, if it is early on in the project (early one-third of a project), are useful. Constructively addressing problem areas in a relaxed manner can be rewarding. Peer evaluation forms may be found that allow one to rank performance (5 = outstanding, 1 = unsatisfactory) versus skills and behaviors (planning, teamwork, time management, motivation, etc.). Many will additionally prompt with questions such as "What are his/her strengths?", "What areas need improvement?", and so forth. If the group is large enough, responses can be anonymous. These same forms may later be used with item 5, if possible. Disbanding a project is seldom warranted, unless it is very early on in the project. Doing nothing is not recommended. If conflicts may be simply solved with reorganization, try this method.

3.3 REPORTING TECHNIQUES: PRESENTATIONS, POSTERS, REPORTS, WEBSITES

Reporting methods vary considerably dependent on the nature of the project (industrial versus academic), the size of the team and of the project, and the expectations of the person(s) to whom the report is being made. Typical reporting techniques involve oral presentations using transparencies or PowerPoint slides or Prezi presentations, poster presentations (especially in academic settings), and formal reports of progress or results (web and/or hard copy). For the student and advisor, a combination of these techniques with the addition of a website can be very useful. (Formal documentation is mandatory in industry, especially if FDA and/or patent considerations are involved.)

3.3.1 Progress Reports: Written

Progress reports, at the lowest level, are fairly simple documentation, generally on paper or in a web section, listing the following items: current status, work completed, current work, and future work. An example progress report might read like the following:

Progress Report: EKG Transmitter Project—Week 7 of 11

Current Status: We recently completed our library and web search for applicable EKG transmitter designs. It appears that the transmitter system designed by Goldman et al. (see references) is out of both a patent and a prime candidate for reverse engineering.

Work Completed: We were able to x-ray the transmitter we borrowed from Dr. Sachs; we were able to do a component count and figure out what brand of battery system they used.

Current Work: B. will meet with EE Prof. Heller this week and go over a chip-level redesign of the amplifier system. C. will review chip-level transmitter systems and encapsulation materials.

Future Work: We appear to be on schedule for the planned end date of next month. Our earlier request for funding has been adequate to obtain the necessary supplies and equipment.

An example progress report (*not*!) follows as an antithesis:

Progress Report: Transmitter Project—Week 12 of 11 (Sorry this is late!)
Current Status: We have been unable to meet with Dr. Wilson as he is out of town. We came by your office but did not find you in to explain our problem. It will not be our fault if we do not complete this project!
Work Completed: We had exams last week, and next week we have spring break, so we have not had time to do anything on this project. It can wait.
Current Work: Packing my bags for spring break.
Future Work: We will place our order for parts when we get back. We are sure X University will quickly get the purchase order in the mail and that the advertised 6-week delivery time is a gimmick. Got to go catch some rays!

Obviously, this is fairly low-level reporting and should serve as a minimum reference. More elaborate reporting schemes would involve additional line items from the original listing of the problem specification (the who, what, where, why … list) and elaborations on the details of current budget levels, current interactions with all interested parties (design, manufacturing, sales, etc.), and a good discussion of status with respect to the original detailed timelines and specifications.

In general, these progress reports should include enough material that your advisor and course instructor can properly evaluate your progress and give you feedback (and funding) as necessary.

In the industrial setting, often in the interest of brevity and time, memos may be constrained to one page or less for status meetings.

3.3.2 Oral Reporting

Oral reporting of progress will include the previously discussed terms at whatever level of complexity is required to convey the information to the audience. PowerPoint presentations will generally convey information better than transparencies if and only if they are properly done. Some general rules to follow are as follows:

- Use your slide area well, but place no more than six to eight lines of information on a page. Text needs to be used sparingly; your job is to fill in the blanks, not read material to your audience.
- Use color and specific colors judiciously. If possible, use color to make a point.
- Use motion (PowerPoint) sparingly. Overuse of materials "flying in" from different areas will quickly lose an audience.
- Learn your style of lecturing; determine if you are a one-slide-per-minute or a one-slide-per-three-minute speaker. Any faster than two to three slides a minute tends to be irritating and likely will lose the audience.
- Use graphics if they assist in understanding the talk.
- If your talk is more than 15 minutes long, consider some way to interest (awaken) the group, via a personal account or a clean joke.
- Be sure you tell the group what you are going to tell them, then tell them, then summarize what you said. (Someone may have slept through two of the three!)
- Be sure that you cover your bases; double check that you have done the *who/what/why …* material.
- Practice your talk. Do not overpractice your talk. Give a dry run if possible in front of a coworker or fellow student whom you can trust to give you valid feedback.

- Consider whether or not to give your audience handouts of your slides in order to retain your message(s).
- If necessary, to avoid nervousness, visualize your audience in their underwear. They are now the ones to be embarrassed!

Sufficient detail should be given in the assigned time frame to allow your course advisor and/or mentor to properly evaluate your current and pending work. You should expect to get feedback from your advisors and other audience members, and you will be expected to actively participate in other student feedback sessions. Presentations using Prezi should obey the same rules as mentioned previously but can provide additional paths for explanation of items as necessary. Caveat: all members of a group should be familiar enough with the project to give any presentation.

3.3.3 Poster Presentations

In academic circles, if you really want to meet people who are interested in your work, and want a one-to-one discussion with them, poster presentations are a good method. For reporting of student work in an academic environment, there seems to be about an even split in the reporting schemes (oral vs. written) used in courses. Some general rules for poster presentations follow:

- Know the size of the poster you are going to place your work on. Typically, a board will be provided that measures 6 or 8 feet wide by 4 feet tall, elevated so that the bottom of the board is approximately 2 feet off the ground. However, if you are reporting in a foreign country, sizes may be 1 meter wide by 2 meters high.
- Plan ahead and lay out your poster presentation on a marked-off floor area before packing it! Or, as is now the more prevalent, design your entire poster using software such as PowerPoint, and try different color schemes and layouts without having to print and test.
- Check to see what method of attachment is allowed. Some situations call for pushpins, others for double-sided tape, and so forth. Bring your own if unsure.
- The title of your poster should appear at the top in large letters, at least 4 to 6 inches in height, readable at a distance of 6 feet. Use uppercase and lowercase; block lettering using all capitals is not good form. If you can do so, put the title on a continuous sheet of paper, rather than on pasted-together single sheets. Author names and affiliations are best placed below this banner, using a slightly smaller font and perhaps italics. If you have access to a poster printer, use it! The visual appeal of a well-designed single-sheet poster is generally far superior to that composed of a series of 8-1/2 inch × 11-inch sheets of paper.
- Subsections should also be legible at a distance and should be abstractions of the primary points of the poster, rather than a text or textbook presentation. Be sure all key points are covered (abstract, introduction … conclusion, references) as necessary.
- Bolded text is generally easier to read, but check this, as not all fonts are easy to read bolded.
- Use color in your text to make a point, if appropriate.
- Your poster should "read" from the top left, in vertical columns, to the bottom right. If you need to change this, be sure to use arrows to interconnect your panels to help guide your readers.
- Color highlighting of your text blocks, which may also be on colored paper, will make your poster more attractive, if the colors are complementary.
- Use pictures, diagrams, cartoons, figures, and so forth rather than text wherever possible. If you are allowed to do so, prepare handout material to supplement your poster. Be sure to include contact information.
- Your poster should be self-explanatory. You may be talking with one person; another can be reading and deciding if they wish to wait to get additional information.

- If appropriate and allowed, bring in additional materials, such as a computer to give a visual demonstration of your work. Use sound appropriately, if at all. Do not induce headaches in yourself and the adjacent poster presenters with inappropriately loud or obnoxious sounds.
- Prepare brief comments for questioners.
- Retrieve your materials at the time stated; otherwise, you may lose the effort put into their development.
- Test-drive your poster with fellow students if possible.
- As appropriate, carry and hand out your business card. Your next job may come of your interactions here.

3.3.4 Websites

For student design projects, the development of a website for the project is a good communication tool, for both the students and the advisors. If done appropriately, the site may also prove of value in a job hunt. Items that should be posted on a website generally include weekly progress reports, monthly oral PowerPoint or Prezi slide shows, end-of-term posters and term papers, and so forth. Optional items, dependent on the course requirements, might be an initial project proposal, Gant charts, 510(k) drafts, patent drafts, safety analyses, design notes, a design history file, a corrected proposal, design notes and calculations, relevant concept maps, business plans, prototype information, and the like. Your instructor should give you guidelines as to the content and timing of each of these items. Design considerations, paralleling those discussed for posters, should also be considered in the layout of the site, such that it is easy to read and to navigate, and documents your team's efforts.

If a project has a possibility of patentability or may involve intellectual property of any kind (or may be considered potentially offensive to some group such as People for the Ethical Treatment of Animals [PETA]), the project website might be password protected. This should be set up so that your team, instructor, and advisor have access. As most website software can also time-stamp each of the page entries, this information may prove of value if a patent is sought on the material contained on your site.

3.3.5 Expectations for Communications

The communication tools discussed involve reporting of your efforts to others. It is important that you understand, before you engage a topic fully, the criteria under which your work will be judged. Each of the previous sections will be discussed in turn.

Weekly written reports, unless made very formal and lengthy, should generally serve as an indicator that the team is on track. If there are immediate needs (financial or otherwise), these should be indicated here and/or via e-mails to the instructor/supervisor. A weekly report might count toward 1% of the term grade and generally will be a function of being posted on time and complete.

Oral reports may also be graded, with instructor feedback on such items as presentation skills and organization, technical content, and determination that the solution being pursued (dependent on the phase of the term) is correct given the demands and constraints of the project at hand. Graded (or not), the oral sessions should provide a means for feedback to the group regarding the conduct of their project. As oral reports will, in general, demand more student effort, they typically will "weigh in" at about three times the value of a written (short) progress report.

In industry, and to a limited extent, in academia, the term "at expectations" is often used. For the academic, it means (generally) that the person has published papers, done service work, done research, and taught at some expected level. In industry, in the context of this text, the term "at expectations" will mean that the person performed at a level of competence expected of his/her experience and pay level in a given situation. In both cases, the term applies to such matters as promotions and pay raises. Poster presentations and final paper evaluations may use this same terminology in an attempt to describe very different outputs from different teams on different tasks. Such a rubric will be discussed next.

When grading design projects, there are several main topical items that must be considered. These will typically include such major topics as engineering goals, creative ability, thoroughness, overall competence in design, clarity of expression, and ethical/societal/political considerations. These topics may then be subdivided (and will be later in this chapter) and judged individually. Evaluations of the subdivisions of each of these may include the terms "at expectations," "above expectations," "below expectations," "not applicable," and "failure." "Failure" is a grade reserved for an item that is mandatory (given the project at hand) but very poorly done (or not at all). "Not applicable" would apply in a case where an item does not need to be considered, at least in depth (for example, a market analysis on a device custom-made for an individual).

Each of the mentioned topical items and their subdivisions will now be discussed in detail.

The "engineering goals" section will typically include three mandatory sections. The first of these is the problem statement, where the evaluator asks the following questions: Did the project have a clear problem definition, identifying constraints and alternatives? Is the work properly based upon customer requirements (often termed "demands and wishes")? Second, did the team prototype, or at least test or predict the performance of, their solution? Has the group considered the manufacturability of the proposed solution? If the product is a database, has it satisfied the requirements of the situation? Is there at least a "proof of concept"? Third, is the problem solution, at whatever level, properly documented? Is there a prototype (preferred)? Is there at least a feasibility analysis? Is the design valid? Does it meet standards? A fourth section, if needed, would include safety, health, and risk analysis for the project outcome. An estimate of environmental impact should be done here, if necessary. Some level of mathematical analysis of risk should be done. A fifth and final section, if needed, should include economic and market considerations. Questions such as the following should be answered: Can it be made? Can people afford it? What is the number of potential users? What are the outcomes of a market survey?

The second section of the poster or report grading form considers creative ability, with a mandatory section evaluating the team's approach to the problem at hand. The questions include the following: Did the team use a logical analysis of the problem at hand? Were alternative solutions considered and evaluated? A second, but not mandatory, consideration would involve determining the originality of the solution, with potential contributions to engineering knowledge and perhaps to the patent literature.

A third section addresses thoroughness of the report. It requires documentation of effort in the form of a project notebook, design file, or other file, such as a website. A second requirement is that a thorough literature and patent search be done, as necessary. Third, a review of applicable standards is optional, as needed.

A fourth section addresses the team's overall competence in design. Required first is proof that proper engineering skills, tools, and techniques were applied to the problem at hand. A second requirement is a demonstrated ability to design a process, system, or component. An optional judgment may involve the scope of the problem tackled and whether the original problem was difficult or not.

The fifth set of judging terms involve clarity of presentation. A first criterion involves the engineering layout of the poster or paper—is it well laid out, easy to read, a good mix of text and pictures? Second, is it a good stand-alone poster or paper, or is additional information needed? Third, does it convince the reader that it is a good solution? Last, and optionally, is there evidence of teamwork in this presentation?

The final, but very important, judging criterion (mandatory) asks about the ethical and political considerations (if any) involved in the solution, in an attempt to judge the aspects of universal design that might not be addressed elsewhere.

This list is a codification of experience in judging design posters and presentations over a period of years. The weighting given to each section is 20%, 20%, 20%, 25%, 10%, and 5%. "At expectations" is defined as 85%; an oval grade of 85% is therefore a *B* in a design course.

This scoring system puts emphasis on overall outcome, rather than perceived quality, such as for a refereed journal. A review form for a journal might include such terms as "content" (20%), "degree of novelty or originality" (10%), "structure of paper" (10%), "quality of text" (10%), and "reviewers' general opinion and comments" (50%), which stresses the reviewer's personal biases.

3.4 INTRODUCTION TO DATABASES

Throughout the design process, data will be generated that may need to be managed in one of two ways—storage in an Excel spreadsheet for later documentation or analysis purposes or storage in a database for similar purposes. Design projects may also involve the design of such a spreadsheet and an overlay of software for data analysis, or design of a database for data storage and subsequent data querying and reporting. At the graduate level, this latter analysis may include such techniques as knowledge discovery, an assembly of techniques used to derive rules from data collected in an environment. This section will introduce the needed concepts involved here prior to your use of them, which may be mandated by the problem at hand.

3.4.1 Excel Spreadsheets

Excel spreadsheets are useful in situations where data fields are essentially "flat"; data can be managed adequately in a simple two-dimensional array or arrays (also known as multiple worksheets). Data that are nonrepetitive can be easily managed using a spreadsheet; data that are repetitive, such as individual patients' demographics for each clinic visit, are better handled with a database. Excel spreadsheets are useful for data sets that do not exceed 32,000 data points in length; after this, typically, data must be chunked in multiple spreadsheets or put into databases. Excel spreadsheets are optimized for simple statistical and other analysis of data and for easily generated plots of data sets. With the use of the Visual Basic Editor, some very useful data entry/calculation programs may be generated.

Such programs may include elementary electrocardiogram analyses, simple lab test statistics and documentation, real-time display of data, clinic utilization statistics, what-if analyses, and so forth. More mundane applications include the storage of design specifications and change orders, verification and validation documentation, and straightforward safety process documentation. The need for these databases will be covered in later chapters.

3.4.2 Databases

Databases are very much in use in the field of design; modern society probably could not function without this invention. Databases are simply a convenient and (should be an) efficient method of storing data, with a high-level language that allows convenient manipulation of the data. Properly designed databases are efficient in storage of data and in fact can reduce costs due to rapid retrieval of data. Redundant entry of information, such as the address of a supplier, is entered only once in a table, rather than in multiple occurrences when the supplier is referenced. Commercial databases include DB2, SQL (Structured Query Language) server, FoxPro, Access, Oracle, Sybase, Informix, and Paradox. With competition, this field will likely narrow in the near future. Each has advantages, dependent on your background and the size of the problem you are trying to solve. Access, for example, might work well in an initial design for a small clinic database, but growth to a larger clinic or the use of multiple simultaneous data entry points would push a designer to SQL or better server systems.

Most databases have the following in common. Data that would otherwise be repeated are keyed in once into a structure termed a table. Data that are entered in a table column (field) generally have a given structure (date, alphanumeric, number, etc.); this can be checked for integrity

as well as for reality during entry. The structure of the database allows for relationships between tables; for example, one table may link to several others (one patient links to multiple cases) or may link to only one other table (one patient, one home address). Tables link through "keys"; such a key might be a patient's social security number or a patient encounter number generated by a clinic. Data entry techniques can involve the generation and utilization of forms. Data extraction techniques involve the use of a query, and the reporting uses another form generated for this use.

Data from databases may be exported for use in spreadsheets, and vice versa; thus, mastery of databases is not necessary for some work in data analysis.

3.4.3 Example: Database Development

In the early 1990s, the pain clinic in a major hospital was simply using paper forms for capture of all information. The forms were used for an initial patient interaction/interview/evaluation (five pages), subsequent psychological patient evaluations if needed (one page each), and subsequent physical/medical evaluations as needed (multiple pages). The initial interaction form held the expected patient demographic information; hospital identification number; referring physician information; pain history; and medical examination information, assessment, diagnosis, and plan of treatment. The psychological assessment plan included a current psychological evaluation, testing results, treatment plan, and other activities. The medical follow-up paperwork included an evaluation of the pain history since the initial visit; treatment for the pain (such as injections, medications, counseling, physical or occupational therapy, biofeedback, relaxation technique training, biofeedback, or transcutaneous electrical nerve stimulation); effects of the treatment; drugs prescribed; pain evaluation; diagnosis; and follow-up plans.

As is common in a circumstance such as this, three main influences pushed this clinic toward the use of a database. The first driving force was that their record-keeping system was entirely dependent on preserving and accessing the paper records that they were generating; lost or incomplete paperwork meant lost revenue. Secondly, the patient population in the clinic was gradually increasing, putting more of a demand on the one secretary/filing clerk available. Third, and most important, was the pressure from insurers to adequately document and report consistently all interventions performed and the reasons for the interventions, at the risk of nonpayment of billed services.

This scenario led to the initial development of an Access database. Three tables were created, one for the initial-visit record system, one for all psychological evaluation/treatment interventions, and one for all medical treatment interventions. The link between all three tables (key) was set to be the patient identifier; the second identifier to keep visits unique was set to be the date of service. An initial system was developed with a paper-form tool for data entry (TeleForms) such that information was entered using block letters and numbers in a standard fill-in-the blank method. A later version was based upon the same information layout but using a direct computer entry method. The disadvantage of the paper-based forms was the need for a paper intermediate step to data entry and the resultant errors due to lack of data entry and misread data forms due to sloppy form copying techniques. The direct terminal entry of data allows the programmer to validate each data entry field as entered and to warn of incomplete data entry on a given patient.

Two main advantages can be gained from development of this database. All insurance information can be adequately entered, documented, and billed for using the report functions in Access. Patient summary letters can be generated for the referring physician also using the report-writing functions of Access.

Example forms used in this database may be seen on the next page (1 of 12 initial intake forms) and the following page, a follow-up visit page.

27115

Vanderbilt University Medical Center
Department of Anesthesiology
VPCC Initial Visit Form

Section 2
Page 1 of 3

Patient Last name:

Patient First name

VUH #: 00000000 - 1

Date:

Medications for Pain

Do you take medicines for pain relief?

- ○ Never
- ○ Yes-less than once a week
- ○ Yes-several times a week
- ○ Yes-one or two times a day
- ○ Yes-three or four times a day
- ◉ Yes-five or more times a day

How long do the pain medicines provide relief?

- ◉ Less than one hour
- ○ 1 - 2 hours
- ○ 2 - 4 hours
- ○ 4 - 6 hours
- ○ More than 6 hours
- ○ I do not take pain medicines

Describe effectiveness of pain medicines, on average.

- ○ Always take the pain away
- ○ Always make the pain less
- ○ Usually take the pain away
- ○ Usually make the pain less
- ◉ Provide little, if any relief
- ○ I do not take pain medicines

Select medications taken for pain (if applicable)

Skeletal Muscle Relaxants:

- ○ Diazepam - VALIUM
- ○ Carisoprodol - SOMA
- ○ Methocarbamol - ROBAXIN
- ○ Chlorzoxazone - PARAFON FORTE
- ○ Cyclobenzaprine - FLEXERIL
- ◉ Baclofen - LIORESAL
- ○ Carisoprodol/Aspirin - SOMA COMPOUND
- ○ Metaxalone - SKELAXIN
- ○ Orphenadrine Ext-rel - NORFLEX
- ○ Orphenadrine/Aspirin/Caffeine - NORGESIC
- ○ Orphenadrine/Aspirin/Caffeine - NORGESIC FORTE

Prophylactic Agents:

- ○ Propranolol - INDERAL
- ○ Propranolol Ext-rel - INDERAL LA
- ○ Acetaminophen/Dichloralphenazone/Isometheptene - MIDRIN
- ○ Divalproex Sodium EC - DEPAKOTE
- ○ Methysergide Maleate - SANSERT
- ○ Ergotamine/Caffeine (not PB) - CAFERGOT
- ○ Dihydroergotamine Inj - D.H.E. 45
- ◉ Sumatriptan - IMITREX

Antidepressants:

- ◉ Amitriptyline - ELAVIL
- ○ Imipramine (not PM) - TOFRANIL
- ○ Doxepin - SINEQUAN
- ○ Lithium Carbonate - LITHONATE
- ○ Amitriptyline/Perphenazine - TRIAVIL
- ○ Trazodone - DESYREL
- ○ Maprotiline - LUDIOMIL
- ○ Desipramine - NORPRAMIN
- ○ Nortriptyline - PAMELOR
- ○ Tranylcypromine - PARNATE
- ○ Nefazodone - SERZONE
- ○ Amoxapine - ASENDIN
- ○ Paroxetine - PAXIL
- ○ Fluvoxamine - LUVOX
- ○ Venlafaxine - EFFEXOR
- ○ Sertraline - ZOLOFT
- ○ Clomipramine - ANAFRANIL
- ○ Bupropion - WELLBUTRIN
- ◉ Fluoxetine - PROZAC

Antianxiety Agents:

- ○ lorazepam - ATIVAN
- ○ Diazepam - VALIUM
- ○ Clorazepate - TRANXENE
- ○ Meprobamate - EQUANIL
- ○ Chlordiazepoxide - LIBRIUM
- ○ Hydroxyzine hcl - ATARAX
- ○ Oxazepam - SERAX
- ○ Alprazolam - XANAX
- ○ Hydroxyzine Pamoate - VISTARIL
- ○ Halazepam - PAXIPAM
- ◉ Buspirone - BUSPAR

Vanderbilt Pain Control Center: Follow Up Visit

14-Jun-96

VUH Number: 0000000-1 [redacted] **Date Evaluated:** 12/13/96

Referring Physician Name: [redacted]

Patient's reported emotional status: Worse

Patient's reported pain intensity since last session is: Worse

Current Subjective Pain Intensity Rating: 99

Patient reports that since last treatment, pain has: increased.

Patient reports pain is now: rarely present - pain every few days or weeks

Patient rested after sleep? yes

Patient's reported use of medications: yes - less than one time per week.

Patient states that the need for medications, if taken, has: decreased moderately

Since initial contact, this many health professionals have been consulted for pain: 13

Patient states that the Pain Clinic has helped: slightly

Via:		
	Injections:	made pain worse
	Medications:	did not help
	Counseling:	helped slightly
	Physical Therapy:	helped moderately
	Biofeedback:	helped considerably
	Relaxation:	helped moderately
	TENS:	helped slightly
	Occupational Therapy:	did not help

Procedures performed on this date:

peripheral nerve block (10644508)
sciatic nerve block (106445)
I.V. regional labetalol block (1064417)
interscalene block (1064415)

EXERCISES

1. Take the material written in this chapter on the rules for a poster session; generate a PowerPoint presentation that conveys the same thoughts in a more vital fashion.
2. For the material on PowerPoint presentations, demonstrate several of the points made using a PowerPoint presentation.
3. Perform a web search for optical character recognition (OCR). Comment on the range of uses for this method of data entry. Comment on some of the disadvantages of this method.
4. Draft a design for a computer method that would contain the relevant information needed to catalog equipment used in a medium-sized biomedical engineering department. At what point would you consider the use of Access over Excel?

5. You are in charge of developing a database for a drop-in clinic for a medium-sized city. What would be some of the key parameters you would need to enter on every patient? Discuss this briefly.
6. Perform a web search using the term "TeleForms"; comment on the uses outlined.
7. Construct a "design team" exercise during or after class to tackle a design exercise. Reporting will be done orally by one of the team members. Members must take one of the following roles: marketing, manufacturing/distribution, legal/safety, engineering, or team leader. Members are responsible for assuming their "roles" on the design team. Design topics could include any one of the following:
   - Design a device to detect sudden infant death syndrome (SIDS) in an infant.
   - Design an automated electroencephalogram (EEG) electrode placement system.
   - Design a device to track Alzheimer's patients' locations.
   - Design a system to track an asthmatic's location and sample the environment for noxious stimuli.
   - Design a head restraint system for race car drivers.
   - Design a pain clinic database.
   - Design a system to quantify male or female arousal in a magnetic resonance imaging (MRI) machine.
   - Any other design suggested by your instructor.

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4 Product Definition

> The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated.
>
> **Plato**

Medical devices are an important part of health care. Yet they are an extraordinarily heterogeneous category of products. The term "medical device" includes such technologically simple articles as ice bags and tongue depressors on one end of the continuum and very sophisticated articles such as pacemakers and surgical lasers on the other end. Perhaps it is this diversity of products coupled with the sheer number of different devices that makes the development of an effective and efficient regulatory scheme a unique challenge for domestic and international regulatory bodies.

The patient is the ultimate consumer of medical devices, from the simplest cotton swab to the most sophisticated monitoring devices. However, with the exception of some over-the-counter products, the medical device manufacturer rarely has a direct relationship with the patient in the marketplace. Unlike many other consumer products, a host of intermediaries influence the demand for medical devices. These intermediaries include policy makers, providers, and payers of health care services.

4.1 WHAT IS A MEDICAL DEVICE?

There are as many different definitions for a medical device as there are regulatory and standards organizations. Though the definitions may differ in verbiage, they have a common thread of content. Two of the more popular definitions are reviewed here.

4.1.1 Food and Drug Administration Definition

Section 201(h) of the Federal Food, Drug, and Cosmetic Act defines a medical device as follows:

> An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:
>
> - recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them
> - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> - intended to affect the structure or any function of the body of man or other animals, and
>
> which does not achieve any of its principal intended purposes through chemical action within or in the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

The Medical Device Amendments of 1976 expanded the definition to include the following:

- Devices intended for use in the diagnosis of conditions other than disease, such as pregnancy
- In vitro diagnostic products, including those previously regulated as drugs

A significant-risk device is one that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant, (2) is used in supporting or sustaining human life, and/or (3) is of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health.

A nonsignificant-risk device is one that does not pose a significant risk.

4.1.2 The Medical Device Directives Definition

The various medical device directives define a medical device as follows:

> Any instrument, appliance, apparatus, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
>
> - diagnosis, prevention, monitoring, treatment or alleviation of disease;
> - diagnosis, monitoring, alleviation of or compensation for an injury or handicap;
> - investigation, replacement or modification of the anatomy or of a physiological process;
> - control of conception;
>
> and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

One important feature of the definition is that it emphasizes the "intended use" of the device and its "principal intended action." This use of the term *intended* gives manufacturers of certain products some opportunity to include or exclude their product from the scope of the particular directive.

Another important feature of the definition is the inclusion of the term *software*. The definition of software will probably be given further interpretation, but it is currently interpreted to mean that (1) software intended to control the function of a device is a medical device; (2) software for patient records or other administrative purposes is not a device; (3) software that is built into a device, for example, software in an electrocardiographic monitor used to drive a display, is clearly an integral part of the medical device; and (4) a software update sold by the manufacturer, or a variation sold by a software house, is a medical device in its own right.

4.2 THE PRODUCT DEFINITION PROCESS

Numerous methods of obtaining new product information exist. They include various ways of collecting data, such as internal sources, industry analysis, and technology analysis. Then the information is screened, and a business analysis is conducted. Regardless of the method of obtaining the information, there are certain key questions:

- Where are we in the market now?
- Where do we want to go?
- How big is the potential market?
- What does the customer really want?
- How feasible is technical development?
- How do we get where we want to go?
- What are the chances of success?

4.2.1 Surveying the Customer

The customer survey is an important tool in changing an idea into a product. The criticality of the survey is exhibited by an estimate that, on the average, it takes 58 initial ideas to get one commercially successful new product to market. It is therefore necessary to talk with various leaders in potential markets to build a credible database of product ideas.

The goal of the customer survey is to match the needs of the customer with the product concept. Quality has been defined as meeting the customer needs. So a quality product is one that does what the customer wants it to do. The objective of consumer analysis is to identify segments or groups within a population with similar needs so that marketing efforts can be directly targeted to them. Several important questions must be asked to find that market that will unlock untold marketing riches:

- What is the *need* category?
- Who is buying, and who is using the product?
- What is the *buying* process?
- How can the market be segmented?

4.2.2 Defining the Company's Needs

While segmentation analysis focuses on consumers as individuals, market analysis takes a broader view of potential consumers to include market sizes and trends. Market analysis also includes a review of the competitive and regulatory environment. Three questions are important in evaluating a market:

- What is the *relevant* market?
- Where is the product in its product life cycle?
- What are the key *competitive* factors in the industry?

4.2.3 What Are the Company's Competencies?

Once a market segment has been chosen, a plan to beat the competition must be chosen. To accomplish this, a company must look at itself with the same level of objectivity with which it looks at its competitors. Important questions to assist in this analysis include the following:

- What are our core competencies?
- What are our weaknesses?
- How can we capitalize on our strengths?
- How can we exploit the weaknesses of our competitors?
- Who are we in the marketplace?
- How does my product map against the competition?

4.2.4 What Are the Outside Competencies?

Once a company has objectively looked at itself, it must then look at others in the marketplace:

- What are the strengths of the competition?
- What are their weaknesses?

- What are the resources of the competition?
- What are the market shares of the industry players?

4.2.5 Completing the Product Definition

There are many other questions that need to be answered in order to complete the product definition. In addition to those mentioned, an organization needs to determine the following:

- How does the potential product fit with our other products?
- Do our current technologies match the potential product?
- How will we differentiate the new product?
- How does the intended use and life of the product affect our plans?

It is also important to consider the marketing mix of products, distribution networks, pricing structure, and overall economics of the product plan. These are all important pieces of the overall product plan as developed in a business proposal. However, the needs and wants of the customer remain the most important information to be collected. One method of obtaining the required customer requirements is quality function deployment (QFD).

4.3 THE QFD PROCESS

QFD is a process in which the "voice of the customer" is first heard and then deployed through an orderly, four-phase process in which a product is planned, designed, made, and then made consistently. The QFD process begins with the wants of the customer, since meeting these is essential to the success of the product. Product features should not be defined by what the developers think their customers want. For clear product definition that will lead to market acceptance, manufacturers must spend both time and money learning about their customer's environments, their constraints, and the obstacles they face in using the product. By fully understanding these influencers, a manufacturer can develop products that are not obvious to its customers or competitors at the outset but will have high customer appeal.

QFD should be viewed from a very global perspective as a methodology that will link a company with its customers and assist the organization in its planning processes. Often, an organization's introduction to QFD takes the form of building matrices. A common result is that building the matrix becomes the main objective of the process. The purpose of QFD is to get in touch with the customer and use this knowledge to develop products that satisfy the customer, not to build matrices.

QFD uses a matrix format to capture a number of issues pertinent and vital to the planning process. The matrix represents these issues in an outline form that permits the organization to examine the information in a multidimensional manner. This encourages effective decisions based on a team's examination and integration of the pertinent data.

The QFD matrix has two principal parts. The horizontal portion of the matrix contains information relative to the customer (Figure 4.1). The vertical portion of the matrix contains technical information that responds to the customer inputs (Figure 4.2).

4.3.1 The Voice of the Customer

The voice of the customer is the basic input required to begin a QFD project. The customer's importance rating is a measure of the relative importance that customers assign to each of the voices. The customer's competitive evaluation of the company's products or services permits a company to observe how its customers rate its products or services on a numerical scale. Any complaints that customers have personally registered with the company serve as an indication of dissatisfaction.

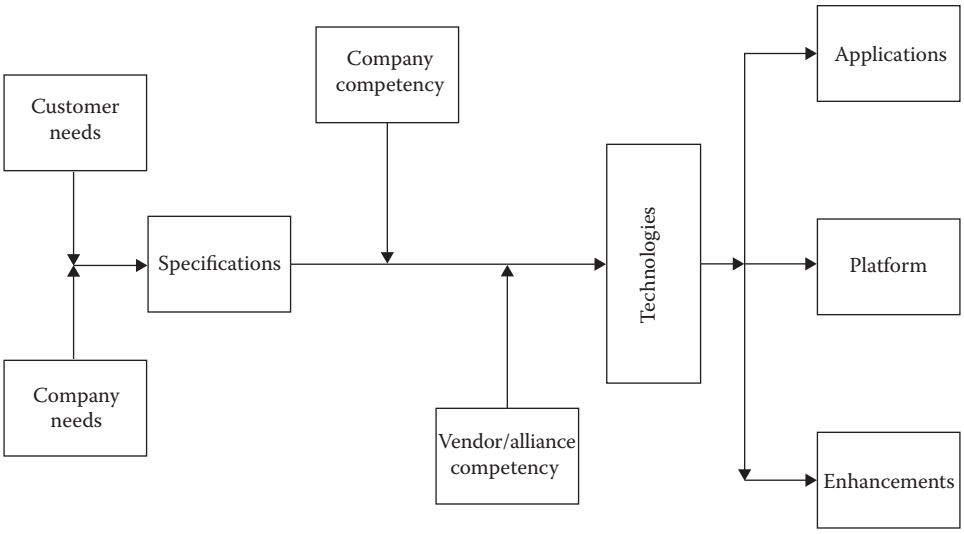

FIGURE 4.1 The product definition process.

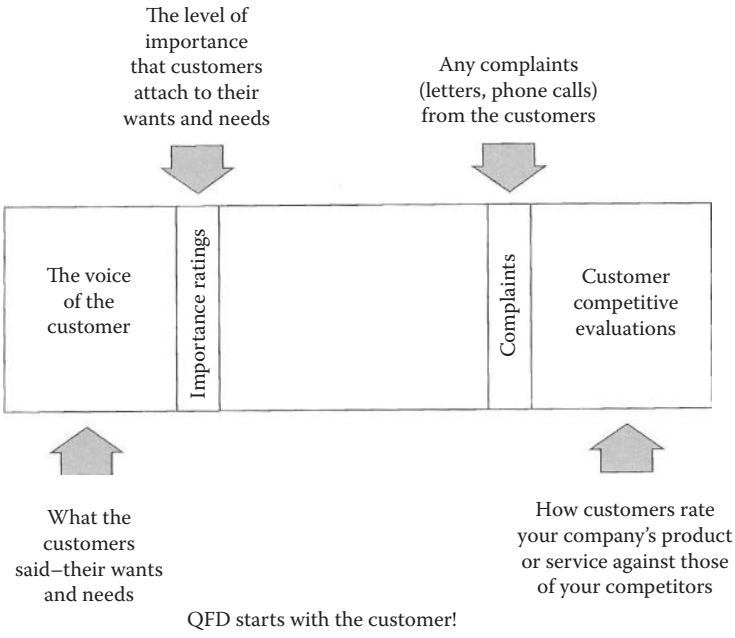

FIGURE 4.2 The customer information portion of the matrix.

4.3.2 The Technical Portion of the Matrix

The first step in developing the technical portion of the matrix is to determine how the company will respond to each voice. The technical or design requirements that the company will use to describe and measure each customer's voice are placed across the top of the matrix. For example, if the voice of the customer stated, "want the control to be easy to operate," the technical requirement might

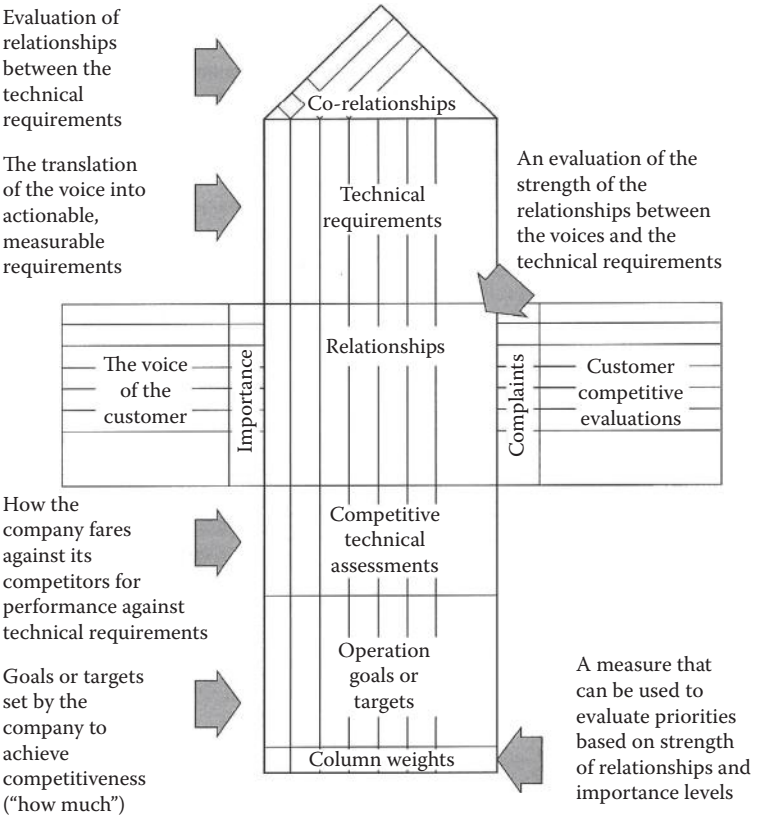

FIGURE 4.3 The technical portion of the matrix.

be "operating effort." The technical requirements represent how the company will respond to its customers' wants and needs.

The center of the matrix, where the customer and technical portion intersect, provides an opportunity to record the presence and strength of relationships between these inputs and action items. Symbols may be used to indicate the strength of these relationships. The information in the matrix can be examined and weighed by the appropriate team. Goals or targets can be established for each technical requirement. Trade-offs can be examined and recorded in the triangular matrix at the top of Figure 4.3. This is accomplished by comparing each technical requirement against the other technical requirements. Each relationship is examined to determine the net result that changing one requirement has on the others.

4.3.3 Overview of the QFD Process

The QFD process is a nine-step process consisting of the following:

- Determining the voice of the customer
- Customer surveys for importance ratings and competitive evaluation
- Developing the customer portion of the matrix
- Developing the technical portion of the matrix
- Analyzing the matrix and choosing priority items
- Comparing proposed design concepts and synthesizing the best
- Developing a part planning matrix for priority design requirements

- Developing a process planning matrix for priority process requirements
- Developing a manufacturing planning chart

In planning a new project or revisions to an old one, organizations need to be in touch with the people who buy and use their products and services. This is vital for hard issues, such as a product whose sales are dependent on the customers' evaluation of how well their needs and wants are satisfied. It is equally crucial for softer issues, such as site selection and business planning.

Once the customers' wants and needs are known, the organization can obtain other pertinent customer information. Through surveys, it can establish how its customers feel about the relative importance of the various wants and needs. It can also sample a number of customers who use its products and competitors' products. This provides the customers' evaluation of both the organization's performance and that of its chief competitors.

Records can be examined to determine the presence of any customer complaint issues. This can be the result of letters of complaint, phone complaints, reports to the Food and Drug Administration (FDA), or other inquiries and comments.

Once this information is available, it can be organized and placed in the horizontal customer information portion of the QFD matrix. The voices of the customers represent their wants and needs—their requirements. These are the inputs to the matrix, along with importance ratings, competitive evaluations, and complaints.

The appropriate team can then begin developing the technical information portion of the matrix. The customers' voices must be translated into items that are measurable and actionable within the organization. Companies use a variety of names to describe these measurable items, such as design requirements, technical requirements, product characteristics, and product criteria.

The relationship between the inputs and the actionable items can then be examined. Each technical requirement is analyzed to determine if action on the item will affect the customer's requirements. A typical question would be the following: "Would the organization work on this technical requirement to respond favorably to the customers' requirements?"

For those items in which a relationship is determined to exist, the team then must decide on the strength of the relationship. Symbols are normally used to denote a strong, moderate, or weak relationship. Some of the symbols commonly used are a double circle, single circle, and triangle, respectively. The symbols provide a quick visual impression of the overall relationship strengths of the technical requirements and the customers' wants and needs.

The team must instigate testing to develop technical data showing the performance of the parent company and its competitors for each of the technical requirements. Once this information is available, the team can begin a study to determine the target value that should be established for each technical requirement. The objective is to ensure that the next-generation product will be truly competitive and satisfy its customers' wants and needs. A comparison of the customers' competitive ranges and the competitive technical assessments helps the organization determine these targets.

Additional information can be added to the matrix depending on the team's judgment of value. Significant internal and regulatory requirements may be added. A measure of organizational difficulty can be added. Column weights can be calculated. These can serve as an index for highlighting those technical requirements that have the largest relative effect on the product.

Once this matrix is complete, the analysis stage begins. The chief focus should be on the customer portion of the matrix. It should be examined to determine which customer requirements need the most attention. This is an integrated decision involving the customers' competitive evaluation, their importance ratings, and their complaint histories. The number of priority items selected will be a balance between their importance and the resources available within the company.

Items selected for action can be treated as a special project or can be handled by use of the QFD matrix at the next level of detail. Any items so selected can become the input to the new matrix. Whereas the first matrix was a planning matrix for the complete product, this new matrix is at a lower level. It concerns the subsystem or assembly that affects the requirement.

The challenge in the second-level matrix (Figure 4.4) is to determine the concept that best satisfies the deployed requirement. This requires evaluation of some design concept alternatives. Several techniques are available for this type of comparative review. The criteria or requirements for the product or service are listed at the left of the matrix. Concept alternatives are listed across the top. The results of the evaluation of each concept versus the criteria can be entered in the center portion.

Once the best concept alternative is selected, a QFD part planning matrix can be generated for the component level (Figure 4.5). The development of this matrix follows the same sequence as that of the prior matrix. Generally, less competitive information is available at this level, and the matrix is simpler. The technical requirements from the prior matrix are the inputs. Each component in the selected design concept is examined to determine its critical part requirements. These are listed in the upper portion. Relationships are examined, and symbols are entered in the center portion. The specifications are then entered for these selected critical part requirements in the lower portion of the matrix.

The part planning matrix should then be examined. Experience with similar parts and assemblies should be a major factor in this review. The analysis should involve the issue of which of the

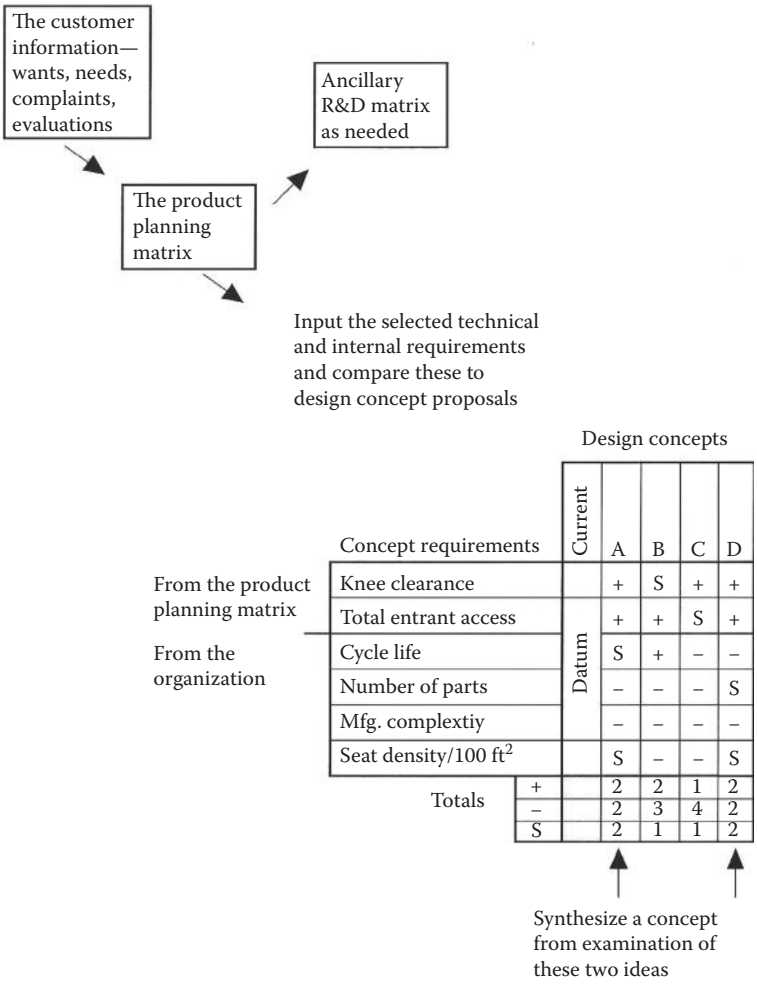

FIGURE 4.4 Second-level matrix. R&D, research and development.

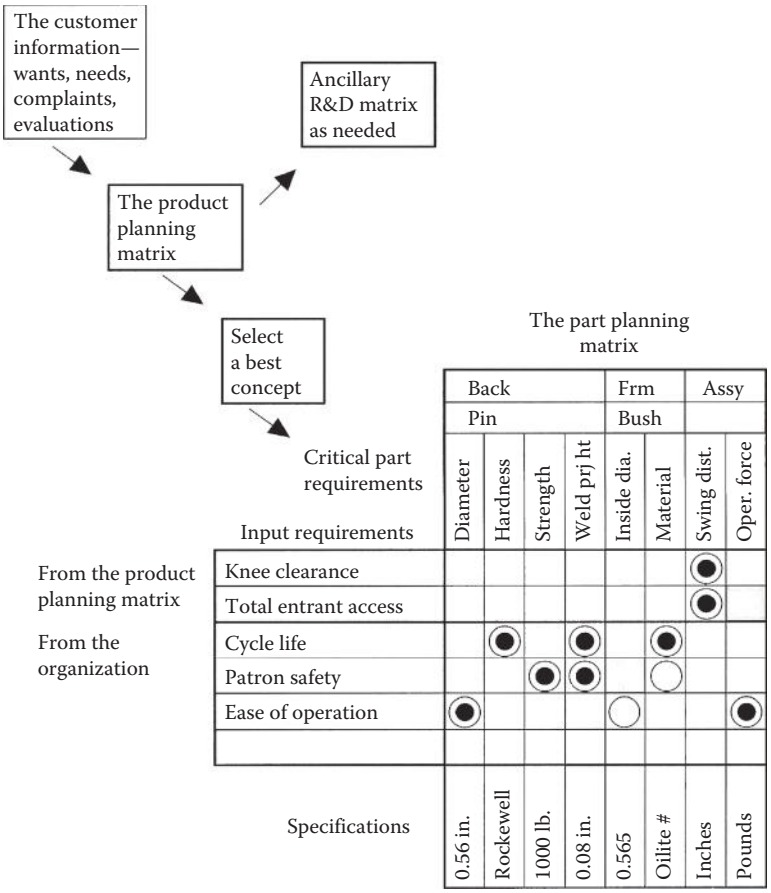

FIGURE 4.5 Part planning matrix.

critical part requirements listed are the most difficult to control or ensure continually. This review will likely lead to the selection of certain critical part requirements that the team believes deserve specific follow-up attention.

If a team believes the selected critical part characteristics are best handled through the QFD process, a matrix should be developed (Figure 4.6) for process planning. The critical part concerns from the part planning matrix should be used as inputs in the left area of the matrix. The critical process requirements are listed across the top. Relationships are developed and examined in the central area. They are recorded in the lower area of the matrix. For example, if a critical part requirement was spot weld strength, one critical process parameter would be weld current. The amount of current would be a critical process parameter to ensure proper spot weld strength. The specification for this critical process requirement would be the amperes of current required to ensure the weld strength.

Upon completion of the planning at the part and process levels, the key concerns should be deployed to the manufacturing level. Most organizations have detailed planning at this level and have developed spreadsheets and forms for recording their planning decisions. The determinations from the prior matrices should become inputs to these documents. Often, the primary document at this level is a basic planning chart (Figure 4.7). Items of concern are entered in the area farthest left. The risk associated with these items is assessed and recorded in the next column. In typical risk assessments, the level of concern and the probability of its occurrence are listed, as are the

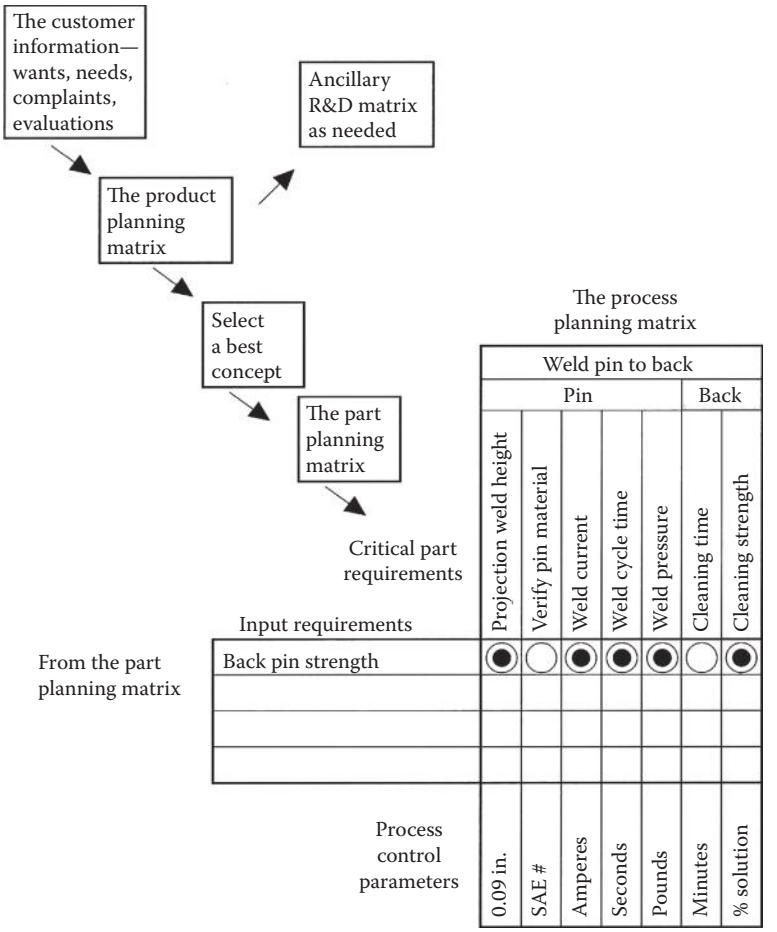

FIGURE 4.6 Process planning matrix.

severity of any developing problems and the probability of detection. These items, along with other concerns, can be used to develop an index to highlight items of significant concern. Other areas in the chart can be used to indicate issues such as the general types of controls, frequency of checking, measuring devices, responsibility, and timing.

4.4 SUMMARY OF QFD

The input to the QFD planning matrix is the voice of the customer. The matrix cannot be started until the customers' requirements are known. This applies to internal planning projects as well as products and services that will be sold to marketplace customers. Use of the QFD process leads an organization to develop a vital customer focus.

The initial matrix is usually the planning matrix. The customers' requirements are inputs. Subsequent matrices may be used to deploy or flow down selected requirements from the product planning matrix for part planning and process planning. Some forms of a manufacturing chart or matrix can be used to enter critical product and process requirements from prior matrices.

The principal objective of the QFD process is to help a company organize and analyze all the pertinent information associated with a project and to use the process to help it select the items demanding priority attention. All companies do many things right. The QFD process will help them focus on the areas that need special attention.

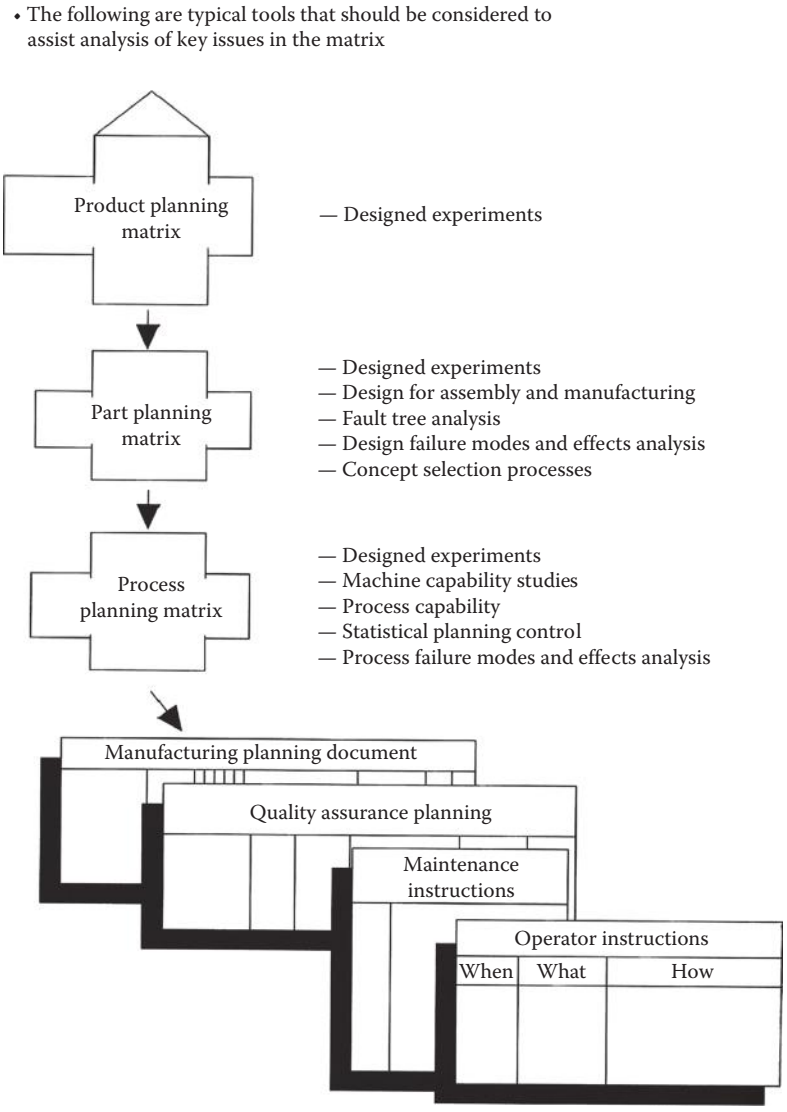

FIGURE 4.7 Manufacturing planning chart.

4.5 REQUIREMENTS, DESIGN, VERIFICATION, AND VALIDATION

As medical products encompass more features and technology, they will grow in complexity and sophistication. The hardware and software for these products will be driven by necessity to become highly synergistic and intricate, which will, in turn, dictate tightly coupled designs. The dilemma is whether to tolerate longer development schedules in order to achieve the features and technology or to pursue shorter development schedules. There really is no choice given the competitive situation of the marketplace. Fortunately, there are several possible solutions to this difficulty. One solution that viably achieves shorter development schedules is a reduction of the quantity of requirements that represent the desired feature set to be implemented. By documenting requirements in a simpler way, the development effort can be reduced by lowering the overall product development complexity. This would reduce the overall hardware and software requirements, which, in turn, reduces the overall verification and validation time.

The issue is how to reduce the number of documented requirements without sacrificing feature descriptions. This can be achieved by limiting the number of product requirements, being more judicious about how the specified requirements are defined, or recognizing that some requirements are really design specifications. A large part of the requirements definition should be geared toward providing a means to delay making decisions about product feature requirements that are not understood until further investigation is carried out.

As stated, verification and validation must test the product to assure that the requirements have been met and that the specified design has been implemented. At worst, every requirement will necessitate at least one test to demonstrate that it has been satisfied. At best, several requirements might be grouped such that at least one test will be required to demonstrate that they all have been satisfied. The goal for the design engineer is to specify the requirements in such a manner as to achieve as few requirements as are absolutely necessary and still allow the desired feature set to be implemented. Several methods for achieving this goal are refinement of requirements, assimilation of requirements, and requirements versus design.

4.5.1 Refinement of Requirements

As an example, suppose a mythical device has the requirement "the output of the analog-to-digital converter (ADC) must be accurate to within plus or minus 5%." Although conceptually this appears to be a straightforward requirement, to the software engineer performing the testing to demonstrate satisfaction of this requirement, it is not as simple as it looks. As stated, this requirement will necessitate at least three independent tests and most likely five tests. One test will have to establish that the ADC is outputting the specified nominal value. The second and third tests will be needed to confirm that the output is within the range of plus or minus 5%. Being a good software engineer, the 5% limit is not as arbitrary as it may seem due to the round-off error of the percent calculation with the ADC output units. Consequently, the fourth and fifth tests will be made to ascertain the sensitivity of the round-off calculation.

A better way to specify this requirement is to state that the output of the ADC must be between *X* and *Y*, where *X* and *Y* values correspond to the original requirement of "plus or minus 5%." This is a better requirement statement because it simplifies the testing that occurs. In this case, only two tests are required to demonstrate satisfaction of this requirement. Test one is for the *X* value, and test two is for the *Y* value. The requirement statements are equivalent, but the latter is more effective because it has reduced the test set size, resulting in less testing time and consequently a potential for the product to reach the market earlier.

4.5.2 Assimilation of Requirements

Consider the situation where several requirements can be condensed into a single equivalent requirement. In this instance, the total test set can be reduced through careful analysis and an insightful design. Suppose that the user interface of a product is required to display several fields of information that indicate various parameters, states, and values. It is also required that the user be able to interactively edit the fields and that key system critical fields must flash or blink so that the user knows that a system critical field is being edited. Further assume that the software requirements document specifies the following: "All displayed fields can be edited. The rate field shall flash while being edited. The exposure time shall flash while being edited. The volume delivered field shall flash while being edited."

These statements are viable and suitable for the requirements specification, but they may not be optimum from an implementation and test point of view. There are three possible implementation strategies for these requirements. First, a "monolithic" editor routine can be designed and implemented that handles all aspects of the field editing, including the flash function. Second, a generic field editor can be designed that is passed a parameter that indicates whether or not the field should

flash during field editing. Third, an editor executive could be designed such that it selects either a nonflashing or flashing field editor routine depending on whether the field was critical or not. Conceptually, based on these requirements statements, the validation team would ensure that (1) only the correct fields can be displayed, (2) the displayed fields can be edited, (3) critical fields blink when edited, and (4) each explicitly named field blinks.

The first "monolithic" design option potentially presents the severest test case load and should be avoided. Since it is monolithic in structure and performs all editing functions, all validation tests must be performed within a single routine in order to determine whether the requirements are met. The validation testing would consist of the four test scenarios presented.

The second design option represents an improvement over the first design. Because the flash/no-flash flag is passed as a parameter into the routine, the testing internally to the routine is reduced because part of the testing burden has been shifted to the interface between the calling and called routines. This is easier to test because the flash/no-flash discrimination is made at a higher level. It is an inherent part of the calling sequence of the routine and therefore can be visually verified without formal tests. The validation testing would consist of test situations 1, 2, and 4 as presented.

The third design option represents the optimum from a test standpoint because the majority of the validation testing can be accomplished with visual inspections. This is possible because the flash/no-flash discrimination is also implemented at a higher level and the result of the differentiation is a flashing field or a nonflashing field. The validation testing would consist of test situations 2 and 4 as presented.

Based on the design options, the requirements could be rewritten in order to simplify testing even further. Assume that the third design option in fact requires less testing time and is easier to test. The requirement statements can then be written in order to facilitate this situation even more. The following requirements statements are equivalent to those aforementioned and in fact tend to drive the design in the direction of the third design option. "All displayed fields can be edited. All critical items being edited shall flash to inform the user that editing is in progress." In this instance, the third design can be augmented by creating a list or look-up table of the fields required to be edited, and a flag can be associated with each that indicates whether the field should flash or not. This approach allows a completely visual inspection to replace the testing because either the field is in the edit list or it is not, and if it is, then it either flashes or it does not. Testing within the routine is still required, but it now is associated with debug testing during development and not with formal validation testing after implementation.

4.5.3 Requirements versus Design

There is agreement that there is a lot of overlap between requirements and design, yet the division between these two is not a hard line. Design can itself be considered a requirement. Many individuals, however, do not appreciate that the distinction between them can be used to simplify testing and consequently shorten overall software development times. Requirements and their specification concentrate on the functions that are needed by the system or product and the users. Requirements need to be discussed in terms of what has to be done and not how it is to be done.

The requirement "hardcopy strip chart analysis shall be available" is a functional requirement. The requirement "hardcopy strip chart analysis shall be from a pull-down menu" has design requirements mixed with the functional requirements. Consequently, there may be times when requirements specifications will contain information that can be construed as design. When developing a requirements specification, resist placing the "how to" design requirements in the system requirements specification and concentrate on the underlying "what" requirements.

As more "how" requirements creep into the requirements specification, more testing must occur on principally two levels. First, there is more detail to test for, and second, but strategically

more important, there is more validation than verification that needs to be done. Since verification is qualitative in nature and ascertains that the process and design were met, low-key activities have been transferred from the visual and inspection methods into validation testing, which is more rigorous and requires formal proof of requirements fulfillment. The distinction of design versus requirements is difficult, but a careful discrimination of what goes where is of profound benefit. As a rule of thumb, if it looks like a description of "what" needs to be implemented, then it belongs in the requirements specification. If it looks like a "how to" description, if a feature can be implemented in two or more ways and one way is preferred over another, or if it is indeterminate as to whether it is a requirements or design, then it belongs in the design specification.

There is another distinct advantage to moving as many "how" requirements to design as possible. The use of computer-aided software engineering (CASE) tools has greatly automated the generation of code from design. If a feature or function can be delayed until the design phase, it can then be implemented in an automated fashion. This simplifies the verification of the design because the automation tool has been previously verified and validated so that the demonstration that the design was implemented is simple.

4.6 THE PRODUCT SPECIFICATION

The product specification is the first step in the process of transforming product ideas into approved product development efforts. It details the results of the customer survey and subsequent interface between the marketing, design engineering, reliability assurance, and regulatory affairs personnel. It specifies what the product will do, how it will do it, and how reliable it will be. To be effective, it must be as precise as possible.

The product specification should be a controlled document, that is, subject to revision-level control, so that any changes that arise are subjected to review and approval prior to implementation. It prevents the all-too-typical habit of making verbal changes to the specification, without all concerned personnel informed. This often leads to total confusion in later stages of development, as the current specification is only a figment of someone's imagination or a pile of handwritten papers in someone's desk.

The specification should also have joint ownership. It should only be written after all concerned departments have discussed the concept and its alternatives and have agreed on the feasibility of the design. Agreement should come from marketing, design engineering, manufacturing, customer service, reliability assurance, and regulatory affairs.

The specification is a detailed review of the proposed product and includes the following:

- The type of product
- The market it addresses
- The function of the product
- The product parameters necessary to function effectively
- Accuracy requirements
- Tolerances necessary for function
- The anticipated environment for the device
- Cautions for anticipated misuse
- Safety issues
- Human factor issues
- The anticipated life of the product
- The reliability goal
- Requirements from applicable domestic or international standards.

Each requirement should be identified with some form of notation, such as brackets and a number. For traceability purposes, each numbered subsection of the specification should start numbering its requirements with the number 1. For example:

5.3.1 Analog-to-Digital Converter
The output of the analog-to-digital converter must be between *X* and *Y* [1].

In parsing the requirements, this particular one would be referred to as 5.3.1-1. Subsequent requirements in this paragraph would be numbered in consecutive order. Requirements in the next paragraph would restart the numbering with 1.

Software programs are available to assist in the parsing process. The software establishes a database of requirements for which a set of attributes are developed that help trace each requirement. Some attributes that might be established include the following:

- Paragraph number
- Date
- Requirement number
- Author of the requirement
- System or subsystem responsible for the requirement
- Type of verification or validation test

The database might appear as in Figure 4.8.

Requirement number	Requirement	Paragraph number	Requirement number	Author	Requirement responsibility	Test type
1221	The machine shall contain no burrs or sharp edges.	3.1	1	Smith	System	Visual
1222	The maximum height of the machine shall be 175 cm.	3.1	2	Smith	System	Valid
1223	The maximum height of the shipping package shall be 185 cm.	3.1	3	Smith	System	Valid
1224	The power supply shall have a maximum inrush current of 7.3 volts.	3.2	1	Jones	Subsystem B	Verification
1225	The power supply shall provide currents of +5 V, +15V, and –15V.	3.2	2	Jones	Subsystem B	Verification
1226	The check valve shall withstand a pressure of 150 PSI.	3.3	1	Thomas	Subsystem C	Verification

FIGURE 4.8 An example section of a specification database.

EXERCISES

1. Do a web search on QFD, report the number and geographical distribution of the information found, and comment on these results.
2. QFD can be used for technical as well as social system development. Find and report on an example of an improved clinic or other system based on QFD principles.
3. A related term is Six Sigma. Do a web search to define this term and then comment on its relationship with QFD.
4. Find and report on any QFD application to a technical problem.
5. Develop the first-level QFD diagram for your next car purchase.
6. You are an employee of Sleep-EZ Inc. You are charged with the development of an inexpensive anesthesia machine for use in third-world countries. Develop a QFD matrix for this task.
7. Develop a set of requirements for the aforementioned anesthesia machine.

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5 Product Documentation

I love being a writer, what I can't stand is the paperwork.

Peter de Vries

Documentation is mandatory, resistance is futile.

Paul H. King

This chapter will cover product documentation requirements in great detail, primarily from a medical device industry viewpoint. Documentation in the medical device and pharmaceutical industry is mandated in the United States under title 21 of the *Code of Federal Regulations* (CFR). The CFR is a codification of the general and permanent rules published in the *Federal Register* by the executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration (FDA). Each title (or volume) of the CFR is revised once each calendar year. A revised title 21 is issued on approximately April 1 of each year and is posted on the FDA website in its entirety.

The additions and revisions to the CFR governing food and drugs used in humans and animals, biologics, cosmetics, medical devices, radiological health, and controlled substances are published in the following "volumes":

- Volume 1: Parts 1–99 (FDA, General)
- Volume 2: Parts 100–169 (FDA, Food for Human Consumption)
- Volume 3: Parts 170–199 (FDA, Food for Human Consumption)
- Volume 4: Parts 200–299 (FDA, Drugs: General)
- Volume 5: Parts 300–499 (FDA, Drugs for Human Use)
- Volume 6: Parts 500–599 (FDA, Animal Drugs, Feeds and Related Products)
- Volume 7: Parts 600–799 (FDA, Biologics; Cosmetics)
- Volume 8: Parts 800–1299 (FDA, Medical Devices)
- Volume 9: Parts 1300–End (DEA and Office of National Drug Control Policy)

21 CFR part 820, for example, defines "Medical Device Quality System Regulation"; a section of this part of the act (part M) defines general and specific record-keeping requirements for medical devices.

All documents and records required by the Quality System Regulation (and the Medical Device Directives [Europe]) must be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to auditors. They must be legible and stored so as to minimize deterioration and to prevent loss. Those stored in computer systems must be backed up and have a disaster plan in effect.

Documents and records deemed confidential by the manufacturer may be marked in order to aid the auditor in determining whether information may be disclosed. All records must be retained for a period of time equivalent to the design and expected life of the device but not less than 2 years from the date of release of the product by the manufacturer.

There are several types of documents that must be kept by every medical device manufacturer. These include the following:

- Business proposal
- Product specification

- Design specification
- Software quality assurance (SQA) plan (SQAP; where applicable)
- Software requirements specification (SRS; where applicable)
- Software design description (SDD; where applicable)

There are four primary types of records that must be kept by every medical device manufacturer. These are the following:

- Design history file (DHF)
- Device master record (DMR)
- Device history record (DHR)
- Technical documentation file (TDF)

Each type of record is discussed in the following sections.

5.1 DOCUMENTS

5.1.1 The Business Proposal

The purpose of the business proposal is to identify and document market needs, market potential, the proposed product and product alternatives, risks and unknowns, and potential financial benefits. The business proposal also contains a proposal for further research into risks and unknowns, estimated project costs, schedule, and a request to form a core team to carry out needed research, to define the product, and to prepare the project plan.

The business proposal usually contains the following:

- Project overview, objectives, major milestones, schedule
- Market need and market potential
- Product proposal
- Strategic fit
- Risk analysis and research plan
- Economic analysis
- Recommendation to form a core project team
- Supporting documentation

5.1.1.1 Project Overview, Objectives, Major Milestones, and Schedule

This portion of the business proposal contains a statement of overall project objectives and major milestones to be achieved. The objectives clearly define the project scope and provide specific direction to the project team.

The major milestones and schedule follow the statement of objectives. The schedule anticipates key decision points and completion of the primary deliverables throughout all phases of development and implementation. The schedule contains target completion dates; however, it must be stressed that these dates are tentative and carry an element of risk. Events contingent upon achievement of the estimated dates should be clearly stated. Examples of milestones include the following:

- Design feasibility
- Patent search completed
- Product specification verified by customers
- Design concept verified through completion of subsystem functional model completed
- Process validation completed

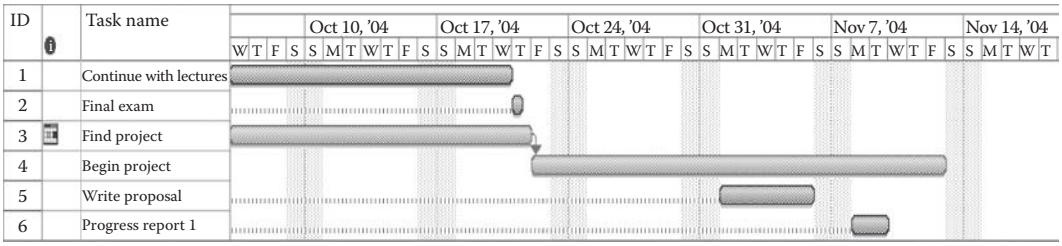

FIGURE 5.1 Gantt chart for a section of a design course.

- Regulatory approval obtained
- Successful launch into territory A (for example)
- Project assessment complete, project transferred to manufacturing and sustaining engineering

This information will generally be in the form of a Gantt chart, such as the one in Figure 5.1 (for a section of a design course). The left-hand side of the Gantt chart lists (in this case) specific tasks to be accomplished; the horizontal axis denotes, via bars, the expected time line for the particular task. Tasks that are dependent on each other, such as "find project," must precede "begin project" and are linked with an arrow. Single events, such as "final exam," occur only at a specific time and do not necessarily have to do with "find project," except that the two events occur once at the same time. Gantt charts are useful for project scheduling, if the number of elements is not large. They are also a good initial planning tool for use when outlining an overall task, such as a redesign of a system and so forth.

5.1.1.2 Market Need and Market Potential

This section of the business proposal defines the customer and clinical need for the product or service and identifies the potential territories to be served. Specific issues that are to be addressed include, but should not be limited, to the following:

- What is the market need for this product, that is, what is the problem to be solved?
- What clinical value will be delivered?
- What incremental clinical value will be added over existing company or competitive offerings?
- What trends are occurring that predict this need?
- In which markets are these trends occurring?
- What markets are being considered, what is the size of the market, and what are the competitive shares?
- What are the market size and the estimated growth rate for each territory to be served?
- What are the typical selling prices and margins for similar products?
- When must the product be launched to capture the market opportunity?
- If competitors plan to launch similar products, what is our assessment of their launch date?
- Have competitors announced a launch date?
- What other similar products compose the market?
- Will the same product fit in all markets served? If not, what are the anticipated gross differences and why? What modifications will be required?
- Is the target market broad-based and multifaceted or a focused niche?
- What are the regulatory requirements, standards, and local practices that may impact the product design for every market to be served?

5.1.1.3 Product Proposal

The product proposal section proposes the product idea that fulfills the market need sufficiently well to differentiate its features and explain how user and/or clinical value will be derived. The product specification is not written, nor does design commence during this phase. It may be necessary to perform some initial feasibility studies, construct nonworking models, perform simulations, and conduct research in order to have a reasonable assurance that the product can be designed, manufactured, and serviced. Additionally, models, simulations, and product descriptions will be useful to verify the idea with customers. If central to your development effort, the elements of a quality function diagram must be developed and evaluated. It is also recommended that several alternative product ideas be evaluated against the "base case" idea. Such evaluation will compare risks, development timelines, costs, and success probabilities.

5.1.1.4 Strategic Fit

This section discusses how the proposed product conforms with (or departs from) stated strategy with respect to product, market, clinical setting, technology, design, manufacturing, and service.

5.1.1.5 Risk Analysis and Research Plan

This section contains an assessment of risks and unknowns, an estimate of the resources needed to reduce the risks to a level whereby the product can be designed, manufactured, and serviced with a reasonable high level of confidence. The personnel resource requirement should be accompanied by the plan and timetable for addressing, researching, and reducing the risks.

The following categories of risks and unknowns should be addressed. Not all of these categories apply for every project. Select those that could have a significant impact on achieving project objectives.

- Technical
  Feasibility (proven, unknown, or unfamiliar?)
  New technology
  Design
  Manufacturing process
  Accessibility to technologies
  Congruence with core competencies
  Manufacturing process capability
  Cost constraints
  Component and system reliability
  Interface compatibility
- Market
  Perception of need in marketplace
  Window of opportunity; competitive race
  Pricing
  Competitive positioning and reaction
  Cannibalization of existing products
  Customer acceptance
- Financial
  Margins
  Cost to develop
  Investment required
- Regulatory
  Filings and approvals (FDA and other regulations)
  Compliance with international standards

Clinical studies; clinical trials
Clinical utility and factors, unknowns
- Intellectual property
  Patents
  Licensing agreements
  Software copyrights
- Requisite skill sets available or needed to design and develop
  Electrical
  Biomedical
  Mechanical
  Software
  Industrial design
  Human factors
  Reliability
- Manpower availability
  Workload of potential members of the team
  Priorities of this and other projects
- Vendor selection
  Quality system
  Documentation controls
  Process capability
  Component reliability
  Business stability
- Schedule
  Critical path
  Early or fixed completion date
  Resource availability
- Budget

The critical path mentioned previously may be derived from the Gantt chart; it is the "path" of activities that are dependent on each other such that the project cannot be completed in any shorter a time than is fixed by their dependencies.

5.1.1.6 Economic Analysis

This section includes a rough estimate of the costs and personnel required to specify, design, develop, and launch each product variant into the marketplace.

5.1.1.7 Core Project Team

This section discusses the formation of a core project team to perform the research required to reduce risks and unknowns to a manageable level, to develop and verify the user specification, and to prepare the project plan.

The requisite skills of the proposed team members should also be outlined. To the extent possible, the following functions should be involved in research, preparation of the user specification, and preparation of the project plan.

- Marketing
- Engineering
- Human factors
- Reliability assurance
- Manufacturing
- Service

- Regulatory
- Quality assurance
- Finance

The approximate amount of time required of each participant as well as incremental expenses should also be estimated. Some examples of incremental expenses include model development, simulation software, travel for customer verification activities, laboratory supplies, market research, and project status reviews.

5.1.2 Product Specification

The product specification is the first step in the process of transforming product ideas into approved product development efforts. It details the results of the customer survey and subsequent interface between the marketing, design engineering, reliability assurance, and regulatory affairs personnel. It specifies what the product will do, how it will do it, and how reliable it will be. To be effective, it must be as precise as possible.

The product specification should be a controlled document, that is, subject to revision-level control, so that any changes that arise are subjected to review and approval prior to implementation. It prevents the all-too-typical habit of making verbal changes to the specification, without all concerned personnel informed. This often leads to total confusion in later stages of development, as the current specification is only a figment of someone's imagination or a pile of handwritten papers on someone's desk.

The specification should also have joint ownership. It should only be written after all concerned departments have discussed the concept and its alternatives and have agreed on the feasibility of the design. Agreement should come from marketing, design engineering, manufacturing, customer service, reliability assurance, quality assurance, and regulatory affairs.

The specification is a detailed review of the proposed product and includes the following:

- The type of product
- The market it addresses
- The technology to be used
- The function of the product
- The product parameters necessary to function effectively
- Accuracy requirements
- Tolerances necessary for function
- The anticipated environment for the device
- Cautions for anticipated misuse
- Safety issues
- Human factors issues
- The anticipated life of the product
- The reliability goal
- Requirements from applicable domestic or international standards

Each requirement should be identified with some form of notation, such as brackets and a number. For traceability purposes, each numbered subsection of the specification should start numbering its requirements with the number 1. For example:

5.3.1 Analog-to-Digital Converter
The output of the analog-to-digital converter must be between *X* and *Y* [1].

In parsing the requirements, this particular one would be referred to as 5.3.1-1. Subsequent requirements in this paragraph would be numbered in consecutive order. Requirements in the next paragraph would restart the numbering with 1.

Software programs are available to assist in the parsing process. The software establishes a database of requirements for which a set of attributes are developed that help trace each requirement. Some attributes that might be established include the following:

- Paragraph number
- Requirement number
- Author of the requirement
- System or subsystem responsible for the requirement
- Date of entry
- Type of verification or validation test

These packages are generally Excel based.

5.1.3 Design Specification

The design specification is a document that is derived from the product specification. Specifically, the requirements found in the product specification are partitioned and distilled down into specific design requirements for each subassembly. The design specification should address the following areas for each subsystem:

- The reliability budget
- Service strategy
- Manufacturing strategy
- Hazard consideration
- Environmental constraints
- Safety
- Cost budgets
- Standards requirements
- Size and packaging
- The power budget
- The heat generation budget
- Industrial design/human factors
- Controls/adjustments
- Material compatibility

In addition, all electrical and mechanical inputs and outputs and their corresponding limits under all operating modes must be defined.

Each performance specification should be listed with nominal and worst-case requirements under all environmental conditions. Typical performance parameters to be considered include the following:

- Gain
- Span
- Linearity
- Drift
- Offset
- Noise
- Power dissipation
- Frequency response
- Leakage
- Burst pressure

- Vibration
- Long-term stability
- Operation forces/torques

As in the product specification, the requirements in the design specification should be identified by a notation such as a bracket and numbers. The parsing tool works well for focusing on these requirements.

5.1.4 Software Quality Assurance Plan

The term *software quality assurance* is defined as a planned and systematic pattern of activities performed to assure that the procedures, tools, and techniques used during software development and modification are adequate to provide the desired level of confidence in the final product. The purpose of an SQA program is to assure that the software is of such quality that it does not reduce the reliability of the device. Assurance that a product works reliably has been classically provided by a test of the product at the end of its development period. However, because of the nature of software, no test appears sufficiently comprehensive to adequately test all aspects of the program. SQA has thus taken the form of directing and documenting the development process itself, including checks and balances.

Specifying the software is the first step in the development process. It is a detailed summary of what the software is to do and how it will do it. The specification may consist of several documents, including the SQAP, the SRS, and the software design specification. These documents serve not only to define the software package but are the main source for requirements to be used for software verification and validation.

A typical SQAP includes the following 16 sections.

5.1.4.1 Purpose

This section delineates the specific purpose and scope of the particular SQAP. It lists the names of the software items covered by the SQAP and the intended use of the software. It states the portion of the software life cycle covered by the SQAP for each software item specified.

5.1.4.2 Reference Documents

This section provides a complete list of documents referenced elsewhere in the text of the SQAP.

5.1.4.3 Management

This section describes the organizational structure that influences and controls the quality of the software. It also describes that portion of the software life cycle covered by the SQAP, the tasks to be performed with special emphasis on SQA activities, and the relationships between these tasks and the planned major checkpoints. The sequence of the tasks shall be indicated as well as the specific organizational elements responsible for each task.

5.1.4.4 Documentation

This section identifies the documentation governing the development, verification and validation, use, and maintenance of the software. It also states how the documents are to be checked for adequacy.

5.1.4.5 Standards, Practices, Conventions, and Metrics

This section identifies the standards, practices, conventions, and metrics to be applied as well as how compliance with these items is to be monitored and assured.

5.1.4.6 Review and Audits

This section defines the technical and managerial reviews and audits to be conducted, states how the reviews and audits are to be accomplished, and states what further actions are required and how they are to be implemented and verified.

5.1.4.7 Test

This section identifies all the tests not included in the software verification and validation plan and states how the tests are to be implemented.

5.1.4.8 Problem Reporting and Corrective Action

This section describes the practices and procedures to be followed for reporting, tracking, and resolving problems identified in software items and the software development and maintenance processes. It also states the specific organizational responsibilities for your company.

5.1.4.9 Tools, Techniques, and Methodologies

This section identifies the special software tools, techniques, and methodologies that support SQA, states their purpose, and describes their use.

5.1.4.10 Code Control

This section defines the methods and facilities used to maintain, store, secure, and document controlled versions of the identified software during all phases of the software life cycle.

5.1.4.11 Media Control

This section states the methods and facilities used to identify the media for each computer product and the documentation required to store the media and protect computer program physical media from unauthorized access or inadvertent damage or degradation during all phases of the software life cycle.

5.1.4.12 Supplier Control

This section states the provisions for assuring that software provided by suppliers meets established requirements. It also states the methods that will be used to assure that the software supplier receives adequate and complete requirements.

5.1.4.13 Records Collection, Maintenance, and Retention

This section identifies the SQA documentation to be retained; states the methods and facilities to be used to assemble, safeguard, and maintain this documentation; and designates the retention period.

5.1.4.14 Training

This section identifies the training activities necessary to meet the needs of the SQAP.

5.1.4.15 Risk Management

This section specifies the methods and procedures employed to identify, assess, monitor, and control areas of risk arising during the portion of the software life cycle covered by the SQAP.

5.1.4.16 Additional Sections as Required

Some material may appear in other documents. Reference to these documents should be made in the body of the SQAP. The contents of each section of the plan shall be specified either directly or by reference to another document.

5.1.5 Software Requirements Specification

The SRS is a specification for a particular software product, program, or set of programs that perform certain functions. The SRS must correctly define all of the software requirements but no more. It should not describe any design, verification, or project management details, except for required design constraints. A good SRS is unambiguous, complete, verifiable, consistent, modifiable, traceable, and usable during the operation and maintenance phase.

Each software requirement in an SRS is a statement of some essential capability of the software to be developed. Requirements can be expressed in a number of ways:

- Through input/output specifications
- By use of a set of representative examples
- By the specification of models

A typical SRS includes the following 11 sections.

5.1.5.1 Purpose

This section should delineate the purpose of the particular SRS and specify the intended audience.

5.1.5.2 Scope

This section should identify the software product to be produced by name; explain what the software product will and, if necessary, will not do; and describe the application of the software being specified.

5.1.5.3 Definitions, Acronyms, and Abbreviations

This section provides the definitions of all terms, acronyms, and abbreviations required to properly interpret the SRS.

5.1.5.4 References

This section should provide a complete list of all documents referenced elsewhere in the SRS or in a separate specified document. Each document should be identified by title, report number if applicable, date, and publishing organization. It is also helpful to specify the sources from which the references can be obtained.

5.1.5.5 Overview

This section should describe what the rest of the SRS contains and explain how the SRS is organized.

5.1.5.6 Product Perspective

This section puts the product into perspective with other related products. If the product is independent and totally self-contained, it should be stated here. If the SRS defines a product that is a component of a larger system, then this section should describe the functions of each subcomponent of the system, identify internal interfaces, and identify the principal external interfaces of the software product.

5.1.5.7 Product Functions

This section provides a summary of the functions that the software will perform. The functions should be organized in a way that makes the list of functions understandable to the customer or to anyone else reading the document for the first time. Block diagrams showing the different functions and their relationships can be helpful. This section should not be used to state specific requirements.

5.1.5.8 User Characteristics

This section describes those general characteristics of the eventual users of the product that will affect the specific requirements. Certain characteristics of these people, such as educational level, experience, and technical expertise, impose important constraints on the system's operating

environment. This section should not be used to state specific requirements or to impose specific design constraints on the solution.

5.1.5.9 General Constraints

This section provides a general description of any other items that will limit the developer's options for designing the system. These can include regulatory policies, hardware limitations, interfaces to other applications, parallel operation, control functions, higher-order language requirements, and criticality of the application, or safety and security considerations.

5.1.5.10 Assumptions and Dependencies

This section lists each of the factors that affect the requirements stated in the SRS. These factors are not design constraints on the software but include any changes to them that can affect the requirements.

5.1.5.11 Specific Requirements

This section contains all the details the software developer needs to create a design. The details should be defined as individual specific requirements. Background should be provided by cross-referencing each specific requirement to any related discussion in other sections. Each requirement should be organized in a logical and readable fashion. Each requirement should be stated such that its achievement can be objectively verified by a prescribed method.

The specific requirements may be classified to aid in their logical organization. One method of classification would include the following:

- Functional requirements
- Performance requirements
- Design constraints
- Attributes
- External interface requirements

This section is typically the largest section within the SRS.

5.1.6 Software Design Description

An SDD is a representation of a software system that is used as a medium for communicating software design information. The SDD is a document that specifies the necessary information content and recommended organization for an SDD. The SDD shows how the software system will be structured to satisfy the requirements identified in the SRS. It is a translation of requirements into a description of the software structure, software components, interfaces, and data necessary for the implementation phase. In essence, the SDD becomes a detailed blueprint for the implementation activity. In a complete SDD, each requirement must be traceable to one or more design entities.

The SDD should contain the following six items of information:

- Introduction
- References
- Decomposition description
- Dependency description
- Interface description
- Detailed design

5.1.6.1 Introduction

The introduction should describe the software being documented, defining the program and its uses in general terms.

5.1.6.2 References

The reference section should allow one to refer to any standards by name (such as IEEE Std 1016-1998) that are necessary to understand the beginning point for analyses that follow.

5.1.6.3 Decomposition Description

The decomposition description records the division of the software system into design entities. It describes the way the system has been structured and the purpose and function of each entity. For each entity, it provides a reference to the detailed description via the identification attribute.

The decomposition description can be used by designers and maintainers to identify the major design entities of the system for purposes such as determining which entity is responsible for performing specific functions and tracing requirements to design entities. Design entities can be grouped into major classes to assist in locating a particular type of information and to assist in reviewing the decomposition for completeness. In addition, the information in the decomposition description can be used for planning, monitoring, and control of a software project. Both hierarchical diagrams and natural language may be used.

5.1.6.4 Dependency Description

The dependency description specifies the relationships among entities. It identifies the dependent entities, describes their coupling, and identifies the required resources. This design view defines the strategies for interactions among design entities and provides the information needed to easily perceive how, why, where, and at what level system actions occur. It specifies the type of relationships that exist among the entities.

The dependency description provides an overall picture of how the system works in order to assess the impact of requirements and design changes. It can help maintenance personnel to isolate entities causing system failures or resource bottlenecks. It can aid in producing the system integration plan by identifying the entities that are needed by other entities and that must be developed first. This description can also be used by integration testing to aid in the production of integration test cases.

5.1.6.5 Interface Description

The entity interface description provides everything designers, programmers, and testers need to know to correctly use the functions provided by an entity. This description includes the details of external and internal interfaces not provided in the SRS.

The interface description serves as a binding contract among designers, programmers, customers, and testers. It provides them with an agreement needed before proceeding with the detailed design of entities. In addition, the interface description may be used by technical writers to produce customer documentation or may be used directly by customers.

5.1.6.6 Detailed Design Description

The detailed design description contains the internal details of each design entity. These details include the attribute descriptions for identification, processing, and data. The description contains the details needed by programmers prior to implementation. The detailed design description can also be used to aid in producing unit test plans.

5.2 RECORDS

5.2.1 The Design History File

The DHF is a compilation of records that describes the design history of a finished device. It covers the design activities used to develop the device, accessories, major components, labeling, packaging, and production processes.

The DHF contains or references the records necessary to demonstrate that the design was developed in accordance with the approved design plans and the requirements of the Quality System Regulation.

The design controls in CFR 21 820.30(j) require that each manufacturer establish and maintain a DHF for each type of device. Each type of device means a device or family of devices that are manufactured according to one DMR. That is, if the variations in the family of devices are simple enough that they can be handled by minor variations on the drawings, then only one DMR exists. It is common practice to identify device variations on drawings by dash numbers. For this case, only one DHF could exist because only one set of related design documentation exists. Documents are never created just to go into the DHF.

The Quality System Regulation also requires that the DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part. As noted, this requirement cannot be met unless the manufacturer develops and maintains plans that meet the design control requirements. The plans and subsequent updates should be part of the DHF. In addition, the QS regulation specifically requires the following:

- The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the DHF.
- Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

Typical documents that may be in, or referenced in, a DHF include the following:

- Design plans
- Design review meeting information
- Sketches
- Drawings
- Procedures
- Photos
- Engineering notebooks
- Component qualification information
- Biocompatibility (verification) protocols and data
- Design review notes
- Verification protocols and data for evaluating prototypes
- Validation protocols and data for initial finished devices
- Contractor/consultant information
- Parts of design output/DMR documents that show plans were followed
- Parts of design output/DMR documents that show specifications were met

The DHF contains documents such as the design plans and input requirements, preliminary input specs, validation data, and preliminary versions of key DMR documents. These are needed to show that plans were created and followed and specifications were met. The DHF is not required to contain all design documents or to contain the DMR; however, it will contain historical versions of key DMR documents that show how the design evolved.

The DHF also has value for the manufacturer. When problems occur during redesign and for new designs, the DHF has the "institutional" memory of previous design activities. The DHF also contains valuable verification and validation protocols that are not in the DMR. This information may be very valuable in helping to solve a problem; pointing to the correct direction to solve a problem; or, most important, preventing the manufacturer from repeating an already tried and found-to-be-useless design.

5.2.2 The Device Master Record

The DMR is a compilation of those records containing the specifications and procedures for a finished device. It is set up to contain or reference the procedures and specifications that are current on the manufacturing floor. The DMR for each type of device should include or refer to the location of the following information:

- Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications
- Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications
- Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment used
- Packaging and labeling specifications, including methods and processed used
- Installation, maintenance, and servicing procedures and methods

It is more important to construct a document structure that is workable and traceable than to worry about whether something is contained in one file or another.

5.2.3 The Device History Record

The DHR is the actual production records for a particular device. It should be able to show the processes, tests, rework, and so forth that the device went through from the beginning of its manufacture through distribution. The DHR should include or refer to the location of the following information:

- The dates of manufacture
- The quantity manufactured
- The quantity released for distribution
- The acceptance records that demonstrate that the device is manufactured in accordance with the DMR
- The primary identification label and labeling used for each production unit
- Any device identification and control numbers used (note: unique device identification [UDI] codes are proposed for most medical devices by the FDA and should be a consideration here).

5.2.4 The Technical Documentation File

The TDF contains all the relevant design data by means of which the product can be demonstrated to satisfy the essential safety requirements that are formulated in the Medical Device Directives. In the case of liability proceedings or a control procedure, it must be possible to turn over the relevant portion of this file. For this reason, the file must be compiled in a proper manner and must be kept for a period of 10 years after the production of the last product.

The TDF must allow assessment of the conformity of the product with the requirements of the Medical Device Directives. It must include the following:

- A general description of the product, including any planned variants.
- Design drawings; methods of manufacture envisaged; and diagrams of components, subassemblies, circuits, and so forth.
- The descriptions and explanations necessary to understand the aforementioned drawings and diagrams and the operations of the product.

TABLE 5.1
Comparison of Record Storage

	Inclusion			
Record	**Design History File**	**Device Master Record**	**Device History Record**	**Technical File**
Agency submittals		X		X
Assembly inspection records		X	X	
Bills of material		X		
Calibration instructions/records		X		
Certificate of Vendor Compliance			X	
Certificates of compliance	X			X
Check sheets			X	
Clinical trial information	X			X
Combined product analysis				X
Component specifications		X		
Declarations of Conformity				X
Design review records	X			
Design specification	X	X		
Design test protocols	X			
Design test results	X			X
Design validation plans	X			
Design validation protocols	X			
Design validation results	X	X		
Design verification plans	X			
Design verification protocols	X			
Design verification results	X			X
Engineering drawings	X	X		
Essential requirements checklists				X
Evaluations of potential vendors	X			
Evaluations of contractors	X			
Evaluations of consultants	X			
Field action reports			X	
Field service reports			X	
Final inspection instructions		X		
Incoming material quality records		X		
Inspection instructions		X		
Inspection plans		X		
Installation instructions		X		
Labeling requirements	X	X		X
Lab notebooks	X	X		
Letters of transmittal		X		
Listings of applicable standards				X
Machining inspection records			X	
Maintenance procedures		X		
Maintenance service reports			X	
MDD design specifications				X
Medical Device Reports (MDRs)			X	
Medical device vigilance reports			X	
Nonconforming material reports			X	
Packaging instructions		X		

(*continued*)

TABLE 5.1 (Continued)
Comparison of Record Storage

	Inclusion			
Record	**Design History File**	**Device Master Record**	**Device History Record**	**Technical File**
Packaging specifications		X		
Postrelease design control change records		X		
Prerelease design control change records	X			
Primary inspection records		X		
Process change control records		X		
Process validation records		X		
Product complaints			X	
Product descriptions		X		X
Product environmental specs		X		
Product manuals		X		
Product routings		X		
Product specifications	X	X		
Product test specifications	X	X		
Production release documentation		X		
Project plans	X			
Project team minutes	X			
Promotional materials		X		
Purchase orders			X	
Quality inspection audit reports		X		
Quality problem reporting sheets			X	
Quality memorandums		X		
Rationale for deviation from standards/ regulations				X
Receipt vouchers			X	
Regulatory submittals		X		
Rework plans	X			
Risk analysis	X			X
Sales order reports			X	
Service specifications		X		
Shipping orders			X	
Software source code	X	X		
Tooling specs/revision log		X		
Work orders			X	

- The results of the risk analysis and a list of applicable standards applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the directives if the standards have not been applied in full.
- In the case of products placed on the market in a sterile condition, a description of the methods used.
- The results of the design calculations and of the inspections carried out. If the device is to be connected to other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when connected to any such device(s) having the characteristics specified by the manufacturer.
- The test reports and, where appropriate, clinical data.
- Labels and instructions for use.

The manufacturer must keep copies of European Community (EC)-type examination certificates and/or the supplements thereto in the TDF. These copies must be kept for a period ending at least 5 years after the last device has been manufactured.

5.3 A COMPARISON OF THE MEDICAL DEVICE RECORDS

A manufacturer will accumulate a large amount of documentation during the typical product development process. The primary question then becomes which documentation is kept and where is it kept? Table 5.1 is an attempt to summarize the typical types of documentation and where they are kept. This is not an exclusive list but serves only as guidance.

EXERCISES

1. Write a one-page business proposal for your design project. Rough out a product specification page and design specification page if applicable.
2. You are going into competition with Johnson and Johnson; you plan to capture 30% of the market for Band-Aids. Do the needed web search to determine your market potential in terms of the US market.
3. The website medicaldesignonline.com has daily columns discussing new medical developments. Go to this website (or a related one) and peruse the industry news section. For one of the recent developments listed, discuss and document the market need. Identify what was obtained from this site versus what you obtain from other site searches.
4. Improper record keeping and other poor practices have bankrupted several medically related firms. Do a web or library search to find such a case. Briefly discuss the case.
5. You are assigned to investigate the consequences of prostectomy. Identify the current market for this operation and the consequences of the operation. Identify a need for improvement relating to your observations.
6. Do a web search using the term "medical device." Detail how many hits are really consulting firms that assist in the structuring of a business proposal or product specification. Print out documentation on two or three of these companies and discuss what the product really is in terms of this chapter. The use of a good search engine (such as Go Network) is recommended; most of the single search engines are not powerful enough.
7. There are a few websites that specialize in determining the market for devices or treatments that target a complex of consequences of lung disease or the like. Most charge a high fee for identifying opportunities for entrepreneurship in the field. Find such a site, document it, and discuss the perceived value of the information.

SUGGESTED READING

ANSI/IEEE Standard 730, *IEEE Standard for Software Quality Assurance Plans*. New York: The Institute of Electrical and Electronics Engineers, Inc., 1989.

ANSI/IEEE Standard 830, *IEEE Guide to Software Requirements Specifications*. New York: The Institute of Electrical and Electronics Engineers, Inc., 1984.

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Silbiger, S., *The Ten Day MBA*. New York: William Morrow and Company, Inc., 1993.
Taylor, J. W., *Planning Profitable New Product Strategies*. Radnor, PA: Chilton Book Company, 1984.
Trautman, K. A., *The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices.* Milwaukee, WI: American Society for Quality Press, 1997.
FDA, *Code of Federal Regulations* Title 21. Washington, DC: Food and Drug Administration, 1996.

6 Product Development

In nothing do men more nearly approach the gods than in giving health to men.

Cicero

A product development process ensures that the design, development, and transfer of a new or modified medical device will result in a product that is safe, effective, and meets user needs and intended use requirements. As shown in Figure 6.1, design controls begin with the approval of product requirements. Product requirements include the needs of the users and patients and intended use of the device. A design and development plan is developed to describe the design and development activities. The product requirements are converted into technical design inputs (System Requirements Specification) that serve as a basis for the design of a medical device. Iterations of the design process result in design outputs that are verified against the design inputs to ensure that the design outputs adequately address the technical design inputs. The finished device is validated to ensure that all product requirements have been addressed. Final product and process specifications are transferred to production. In the course of the design process, documentation pertaining to the design of the finished device is maintained in a design history file (DHF). Changes to the device design are managed and controlled both prior to and after design transfer until retirement. Risk management is performed simultaneously with device design and development. Formal design reviews are conducted at appropriate points to evaluate the adequacy of the design to fulfill all requirements.

6.1 PRODUCT REQUIREMENTS

The product concept must be documented. This can range from a brief description for products similar to existing ones to a formal document, such as a marketing requirements document, for new and complex products.

Product requirements include the needs of the users and patients and address the intended use of the device. They also include the following requirements, if applicable:

- User/patient/clinical performance characteristics
- Privacy and security
- Safety
- Regulatory
- Quality
- Reliability
- Compatibility with accessories/auxiliary devices or products
- Compatibility with the intended environment
- Human factors
- Physical characteristics
- Sterility
- Manufacturability
- Serviceability
- Labeling, packaging, storage
- Requirements for intended markets (domestic or international)

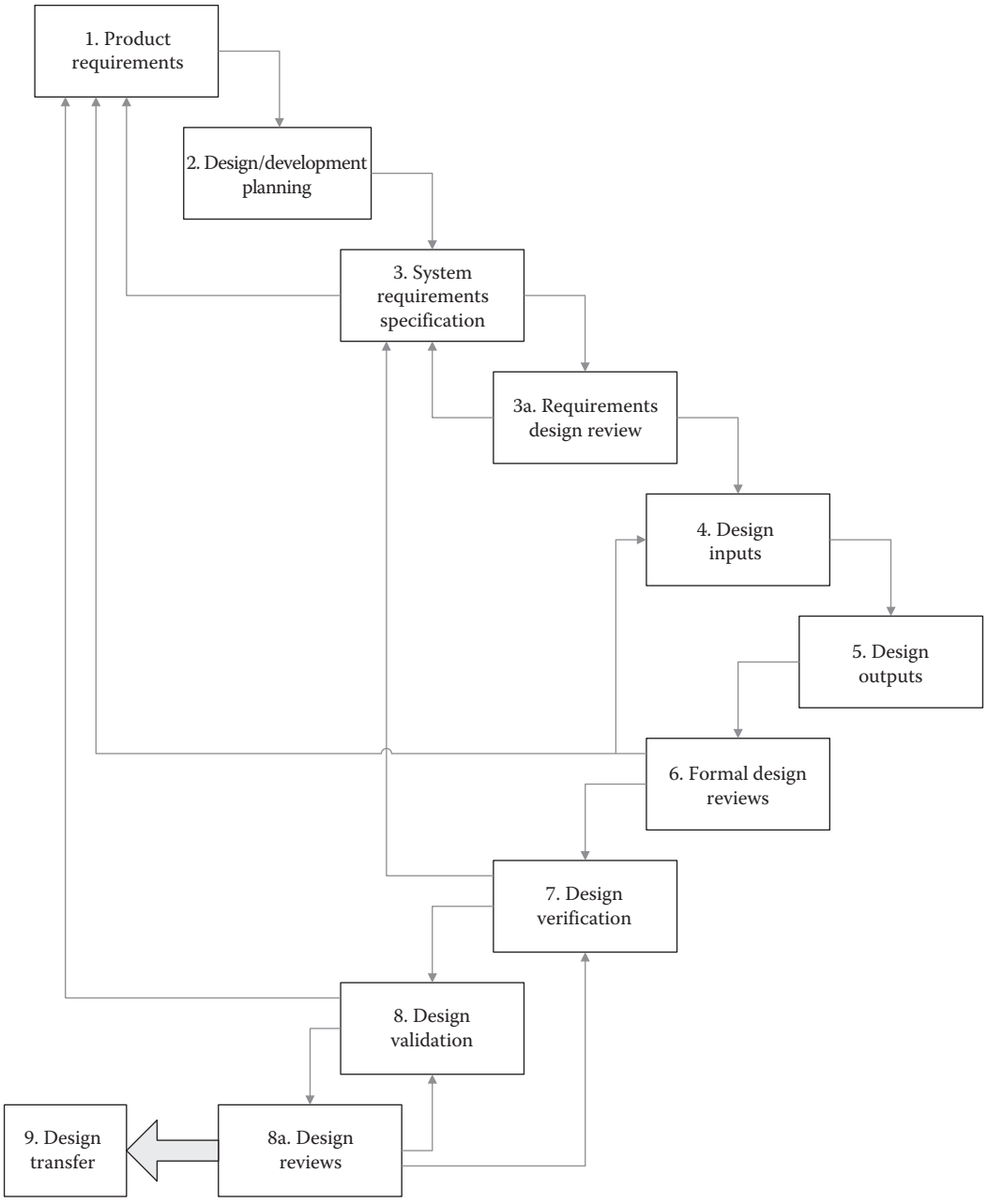

FIGURE 6.1 Product development process.

The types of information described may come from a variety of sources such as market research studies, customer complaints, field failure analysis, service records, regulatory needs, user interviews, and customer satisfaction analysis. Input sources used shall be documented. Requirements that are essential to the quality, safety, and proper function must be identified. Product requirements are reviewed, approved, and documented in the DHF.

6.2 DESIGN AND DEVELOPMENT PLANNING

Each product program must establish and maintain a plan(s) that describes or references the design and development activities and defines responsibility for implementation. It identifies and describes the interfaces with different groups or activities that provide, or result in, input to the design and development process. The design and development plan is reviewed, updated, and approved as the design and development of a product evolves.

The design and development plan describes how the different design control requirements are to be met. It includes all major activities, design deliverables, responsibilities, resources, and associated timelines for the development of a product. The program team creates the design and development plan and reviews, updates, and approves the plan as design and development evolves. The design and development plan resides in the DHF, and any changes made to the plan also reside in the DHF.

6.2.1 Design and Development Plan

The following elements are addressed, if applicable, in the design and development plan. The applicability of these elements is determined by the program team, and justification is provided for elements deemed not applicable.

6.2.1.1 Program Goals

High-level goals and objectives of the product are described, that is, what is to be developed and other considerations that communicate the size, scope, and complexity of the product development project.

6.2.1.2 Design and Development Elements

Design and development elements refer to different categories of activities performed in the design of a medical device from design inputs through design transfer to manufacturing and service. The design and development plan describes the different elements including their scope and planned approach to fulfill the requirements of each element. The timelines for the activities associated with the different elements are incorporated in the design and development schedule. Required design and development elements include the following:

- Design input

  Identify the design inputs that will be used during design and development. Identify the activities for translating user needs and product requirements into technical design inputs.
- Design activities

  Identify the design activities anticipated to develop the product including those performed by suppliers and contractors. Include anticipated design iterations and contingencies. Design activities shall include, if applicable, the following:
  - Development of new technologies
  - Reuse of existing technologies
  - Definition of system, subsystem, and module architectures
  - Design characterization and definition of design parameters
  - Component selection and supplier quality
  - Development and testing of subsystem prototypes and modules
  - System integration and testing
  - Design for reliability and risk analyses
  - Software design and development (including configuration management)
  - Activities to develop other design outputs
  - Technical assessments
  - Regulatory strategy and submissions

- Design outputs
  Identify the design output elements that will be developed and the activities for developing them.
- Formal design reviews
  Identify the timing, intended content, and reviewers for the formal design review(s) that will be conducted during the product program. Each product program should have at least one formal design review. Formal design review(s) should be conducted to review, at a minimum, the following:
  - Completed design inputs
  - Completed design outputs
  - Completed design validation
- Design verification
  Identify and provide an overview of the verification activities, for developing objective evidence that design input requirements have been met, including activities for the development of verification plans, test methods, testing, reporting, and reviewing results.
- Design validation
  Identify and provide an overview of the validation activities for developing objective evidence that the device design meets product requirements, including activities for the development of validation plans, test methods, testing, reporting, and reviewing results.
- Design transfer
  Identify the activities for translating the device design to production and service specifications and for transferring it to the manufacturing and service operations. Identify the requirements to be considered in selecting a manufacturing site or identify the manufacturing site, if known.
- Design change control
  Identify the mechanism(s) and responsibilities for reviewing and approving design changes.
- Design history file
  Identify the location of the product program DHF contents to allow ease of access. Reference other DHFs (and their locations) that may be leveraged for the product being developed. Identify key milestones at which all the documents in the DHF shall be brought up to date and be revision controlled, as appropriate.
- Risk management
  Summarize the methods and activities that will be used to address potential product and process hazards to customers through risk management.

6.2.1.3 Organizational and Key Interfaces

Identify the key individuals/functions responsible for performing the design and development tasks, including cross-functional program team members and external resources, such as suppliers, contractors, or partners. At a minimum, define the roles for research and development (R & D), marketing, manufacturing, quality, reliability, regulatory, and service.

6.2.1.4 Deliverables and Responsibilities

Identify the design control deliverables for the product program and indicate the personnel responsible for completing them. The deliverables to be addressed are dependent on the size, scope, and complexity of the product program and must be defined by the program team leader and program team.

6.2.1.5 Design and Development Schedule

Based on the size, scope, complexity of the product program, the design and development elements, and the list of deliverables, prepare a design and development schedule. The schedule is specified

at the level of detail necessary for carrying out major activities, completing program deliverables, and addressing design control requirements. Identify these activities, deliverables, the responsible individual/function, resources required, and the associated due dates. Indicate which activities are concurrent, sequential, and dependent on other activities. Identify the major milestones and formal design reviews.

6.2.1.6 Approval of Design and Development Plan

The plan is completed and approved by the program team prior to the commencement of detailed design.

6.2.1.7 Incorporation of Updates to Design and Development Plan

Changes to the design and development plan are reviewed and approved at key milestones as determined by the program team. The design and development plan identifies the number and timing of plan reviews by the program team. The plan is revision controlled.

6.3 SYSTEM REQUIREMENTS SPECIFICATION

Product requirements are translated into the system requirements specification that specifies what the design must do to an engineering level of detail. Inputs from results of risk management are included.

The system requirements specification includes the following types of requirements:

- Functional requirements: these requirements specify what the device does, focusing on the operational capabilities of the device and processing of inputs and the resultant outputs.
- Physical and performance requirements: these requirements specify how much or how well the design must perform, addressing such issues as speed, strength, size, weight, response times, accuracy, precision, limits of operation, device safety, reliability, and so forth.
- Interface requirements: these requirements specify characteristics that are critical to compatibility with external systems (including user and/or patient interface).
- System architecture: these requirements specify relationships among logical functions, physical systems/subsystems, and interfaces.
- Software requirements (if applicable): these requirements specify product functionality to be implemented through software and the functional, performance, interface, and safety requirements for the software subsystem(s).

Where appropriate, the system requirements specification should include additional design details in areas such as specification limits and tolerance, risk management, toxicity and biocompatibility, electromagnetic compatibility (EMC), human factors, software, chemical characteristics, reliability, regulatory requirements, manufacturing processes, service design requirements, and testing. If the design logically decomposes into subsystems, the system requirements specification may be used to generate subsystem-level requirements. Traceability of the system requirements specification to product requirements and design outputs is maintained. Requirements that are essential to quality, safety, and proper function are identified.

Incomplete, ambiguous, or conflicting requirements are identified and resolved using the following mechanism:

- The program team reviews design inputs to identify and resolve incomplete, ambiguous, or conflicting requirements.
- Any remaining incomplete, ambiguous, or conflicting requirements are addressed in a formal design review.

The system requirements specification is reviewed, approved, and documented in the DHF.

6.4 DESIGN INPUT

Each product program must establish design inputs to ensure that design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. There should be a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements are documented, reviewed, and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, is documented.

Each product program establishes product requirements. Product requirements include the needs of the users and patients and intended use of the device. Product requirements are translated into technical design inputs that are specified at an engineering level of detail.

Product requirements and the system requirements specification obtained from the translation of product requirements constitute design input for the product program. Traceability is maintained to ensure that product requirements are linked to the corresponding system requirements specification and design outputs.

6.4.1 Product Requirements

The product concept is documented, and the higher-level product requirement is codified. This can range from a brief description for products similar to existing ones to a formal document, such as a marketing requirements document, for new and complex products. Product requirements include the needs of the users and patients and address the intended use of the device. They also include the following requirements, if applicable:

- User/patient/clinical performance characteristics
- Privacy and security
- Safety
- Regulatory
- Quality
- Reliability
- Compatibility with accessories/auxiliary devices or products
- Compatibility with the intended environment
- Human factors
- Physical characteristics
- Sterility
- Manufacturability
- Serviceability
- Labeling, packaging, storage
- Requirements for intended markets (domestic or international)

The types of information described above may come from a variety of sources such as market research studies, customer complaints, field failure analysis, service records, regulatory needs, user interviews, and customer satisfaction analysis. Input sources used are documented. Requirements that are essential to quality, safety, and proper function are identified. Product requirements are reviewed, approved, and documented in the DHF.

6.5 DESIGN OUTPUT

Design outputs are the results of the design effort. Initial design activities result in intermediate design outputs. As design and development progresses, intermediate design outputs evolve into final design outputs that form the basis of the device master record (DMR).

The following general requirements apply to design outputs:

- Design outputs are maintained and documented such that they can be evaluated for conformance to design inputs. Traceability of design outputs to design inputs shall be maintained.
- Acceptance criteria for design outputs are established to enable verification and validation. Acceptance criteria related to device performance, such as accuracy, reliability, and so forth, are defined with tolerance limits.
- Design outputs that are essential to the quality, safety, and proper functioning of the device are identified. These outputs are identified by design and risk analysis.

6.5.1 Intermediate Design Output

Intermediate design outputs are deliverables that define and characterize the design. The following intermediate design outputs are created and recorded in the DHF as applicable:

- Preliminary design specifications
- Models and prototypes
- Software source code
- Risk analysis results
- Traceability documents
- Biocompatibility and bioburden test results
- Other intermediate design outputs as appropriate

6.5.2 Final Design Output

Final design outputs form the basis of the DMR, are recorded in the DHF, and shall include the following elements:

- Device specifications
- Device drawings
  - Component
  - Assembly
  - Finished device
- Composition, formulation, component specifications
  - Subassembly specifications (if applicable)
  - Component and material specifications
  - Product configuration documents
  - Parts list
  - Bill of materials
- Software specifications (if applicable)
- Software machine code, such as a diskette or master EPROM
- Production process specifications
- Critical production process specifications
- Equipment specifications
- Production methods and procedures
  - Test protocols
  - Work instructions
- Production environmental specifications

- Quality assurance procedures and specifications
  - Acceptance criteria
  - Purchasing and acceptance requirements
  - Quality assurance equipment to be used
- Packaging and labeling specifications including methods and processes used
- Installation, maintenance, and servicing procedures and methods
  - Installation instructions
  - Service and maintenance instructions

6.6 FORMAL DESIGN REVIEW

Formal documented reviews of design results should be planned and conducted at appropriate stages of device design and development. Participants at these reviews include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any necessary specialists. The results of these reviews are documented in the DHF and include identification of the design, date, and individual(s) performing the review.

Formal design reviews are performed at major decision points or milestones in the design process as specified by the design and development plan. They are intended to be a systematic assessment of design results and to provide feedback to designers on existing or emerging problems. Each formal design review must ensure that design outputs meet design inputs. They may also be used as a "stage-gate" session where continued development is or is not continued.

6.6.1 Action Tracking and Issue Resolution

Action items identified in formal design reviews are tracked to completion. Objective evidence of completion is documented. Resolution of issues may involve a design change, a requirements change, and/or analysis justifying no action. The program team is responsible for ensuring that all issues and differences identified during the formal design review are resolved. Unresolved issues are escalated to management for resolution, guidance, or additional resources.

6.7 DESIGN VERIFICATION

Design verification is performed to confirm that the design output meets design input requirements. The results of design verification are documented in the DHF and include the identification of the design, test methods, date, and individual(s) performing the verification.

6.7.1 Design Verification Plan

Plans for subsystem- and system-level verification activities need to be developed. Typically, subsystem-level verification activities, if applicable, are performed before system-level verification activities. The plan identifies the timing and types of verification activities to be performed, the personnel performing the activities, and equipment to be used. Design verification includes the following:

- Verification of requirements (system and subsystem level where appropriate)
- Verification of labeling, packaging, on-screen displays, printouts, and any other similar specifications

There must be confirmation that acceptance criteria have been established prior to the performance of verification. As appropriate, necessary statistical techniques to confirm the acceptance criteria must be identified.

Traceability is maintained between design outputs, their corresponding design inputs, and verification activities to confirm that design outputs meet the system requirements specification. Verification plans must be reviewed and approved.

6.7.2 Design Verification Test Methods

Test and inspection methods (protocols/scripts/procedures) for design are developed, documented, and approved before use. Verification methods include the following, if applicable:

- Integration testing
- Functional testing
- Accuracy testing
- System and subsystem performance testing
- Software testing such as unit/module, integration, system-level, and regression testing
- Package integrity tests
- Biocompatibility testing of materials
- Bioburden testing of products to be sterilized

Verification may be done by analysis where testing is not appropriate or practical, such as the following:

- Tolerance analysis
- Worst-case analysis of an assembly to verify that components are derated properly and not subject to overstress during handling and use
- Thermal analysis of an assembly to assure that internal or surface temperatures do not exceed specified limits
- Fault tree analysis of a process or design
- Failure modes and effects analysis of a process or design
- Finite element analysis
- Software source code evaluations such as code inspections and walk-throughs
- Comparison of a design to a previous product having an established history of successful use
- Clinical evaluation analysis

Test methods are based on generally acceptable practices for the technologies employed in similar products, such as compendia methods (e.g., American Society for Testing Materials [ASTM], International Electrotechnical Commission [IEC], Institute of Electrical and Electronic Engineers [IEEE], National Institute of Standards and Technoloy [NIST]). Test methods include defined conditions for testing. The test equipment used for verification must be calibrated and controlled according to quality system requirements. Repeatability and reproducibility of test procedures are determined. Technical comments about any deviations or other events that occur during testing shall be documented.

6.7.3 Design Verification Report

A design verification report summarizes the results of verification activities. Detailed verification results, such as original data, are contained or referenced in the report. The design verification report and referenced documents are included in the DHF. Documentation of the results includes

identification of the design, method(s), date, and the individual(s) performing the verification. Review and approve verification results to ensure that acceptance criteria have been met and all discrepancies identified by verification are resolved.

6.8 DESIGN VALIDATION

Design validation is performed to ensure that the device design conforms to user needs and intended uses. Design validation is performed under defined operating conditions on initial production units, lots, batches, or their equivalents and shall include testing of production units under actual or simulated use conditions. Design validation includes software validation and risk analysis, where appropriate. The results of validation are documented in the DHF and include the identification of the design, test methods, date, and individual(s) performing the validation.

6.8.1 Design Validation Plan

The design validation plan identifies the timing and types of validation activities to be performed, performance characteristics to be assessed, personnel performing the tests, and equipment to be used in validating the device.

Design validation includes the following, if applicable:

- Software validation
- External evaluations
- Process validation
- Risk analysis
- Validation of labeling and packaging

There must be confirmation that acceptance criteria have been established prior to the performance of validation. As appropriate, identify necessary statistical techniques to confirm the acceptance criteria.

Validation needs to be performed on initial production units, lots, batches, or their equivalents and done under actual or simulated use conditions. Where equivalent materials are used for design validation, such materials must be manufactured using the same methods and specifications to be used for commercial production. Justification needs to be provided to establish why the results are valid and must include a description of any differences between the manufacturing process used for the equivalent device and the process intended to be used for routine production. Validation must be complete before commercial distribution of the product.

Traceability must be maintained between design outputs, their corresponding design inputs, and validation activities to confirm that design outputs meet product requirements. Validation plans are reviewed for appropriateness and completeness and to ensure that user needs and intended use(s) are being addressed.

6.8.2 Design Validation Test Methods

Test and inspection methods (protocols/scripts/procedures) for design validation must be developed, documented, and approved before use. Validation methods include the following, if applicable:

- Simulated use testing
- Testing confirming product data sheets, users' manual, product labels, and user interface screens
- Safety testing

Validation may be done by analysis where testing is not appropriate or practical, such as the following:

- Historical comparisons to older devices
- Scientific literature review
- Failure modes and effects analysis of a design or process
- Workload analysis
- Alternative calculations
- Auditing design output
- Comparison of a design to a previous product having an established history of successful use

Validation is performed according to a written protocol that includes defined conditions for testing and simulations of expected environmental conditions such as temperature, humidity, shock, and vibration, and environmental stresses encountered during shipping and installation.

The test methods identified in the plan are based on generally acceptable practices for the technologies employed in similar products. The test equipment used for validation is calibrated and controlled according to quality system requirements. Repeatability and reproducibility of test procedures is determined.

6.8.3 Design Validation Report

A design validation report summarizing the results of validation activities is developed. Detailed validation results, such as original data, are contained or referenced in the report. The design validation report and referenced documents are included in the DHF.

Documentation of the results includes identification of the design, method(s), date, and the individual(s) performing the validation. Validation results are reviewed and approved to ensure that acceptance criteria have been met and all discrepancies identified by verification are resolved.

6.9 DESIGN TRANSFER

Design transfer ensures that the device design is correctly translated into production specifications and that the finished device is successfully transferred from design to production and service. Production specifications ensure that devices are repeatedly and reliably produced within product and process capabilities.

EXERCISES

1. From the quality function deployment developed for the anesthesia machine in Chapter 4, develop a list of requirements for the device.
2. Develop a list of design inputs for the anesthesia machine above, based on the requirements.
3. Develop a list of risks involved in the use of the anesthesia machine.
4. How would the activities for the software portion of the anesthesia machine differ from the hardware portion of the device?
5. Develop a list of design outputs for the anesthesia machine and the activities necessary to accomplish them.
6. What verification activities would be necessary to prove your requirements?
7. Identify the activities for translating the anesthesia machine design to production and service.
8. Identify the requirements to be considered in selecting a manufacturing site for the anesthesia machine.

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7 Hardware Development Methods and Tools

> The future of the aircraft industry is still the responsibility of the engineer. Money alone never did and never will create anything.
>
> ***Aviation Week***

Design input provides the foundation for product development. The objective of the design input process is to establish and document the design input requirements for the device. The design input document is as comprehensive and precise as possible. It contains the information necessary to direct the remainder of the design process. It includes design constraints but does not impose design solutions.

Once the documentation describing the design and the organized approach to the design is complete, the actual design work begins. As the design activity proceeds, there are several failure-free or failure-tolerant tools that must be considered to make the design more reliable. Each is important and has its own place in the design process.

7.1 DESIGN FOR SIX SIGMA

Six Sigma is a revolutionary business process geared toward dramatically reducing organizational inefficiencies that translate into bottom line profitability. It started in the 1980s at Motorola and spread to such organizations as Allied Signal, Seagate, and General Electric. The process consists of five steps known as DMAIC:

- Define
- Measure
- Analyze
- Improve
- Control

By systematically applying these steps, with the appropriate tools, practitioners of this approach have been able to save substantial dollars.

The basis of Six Sigma is measuring a process in terms of defects. The statistical concept of Six Sigma means your processes are working nearly perfectly, delivering only 3.4 defects per million opportunities (DPMO). Most organizations in the United States are operating at a 3–4 sigma quality level. This means they could be losing up to 25% of their total revenue due to processes that deliver too many defects, defects that take up time and effort to repair as well as making customers unhappy.

The central idea of Six Sigma management is that if you can measure the defects in a process, you can systematically figure out ways to eliminate them, thus approaching a quality level of zero defects. The goal is to get the maximum return on your Six Sigma investment by spreading it throughout your company, continuing to train employees in the Six Sigma methodology and tools to lead process improvement teams, and sustaining the exponential gains you achieve by

continuing to improve. One area the methodology of Six Sigma can be extended to is product design.

Design for Six Sigma (DFSS) is an approach to designing or redesigning products and/or services to meet or exceed customer requirements and expectations. Like its parent Six Sigma initiative, DFSS uses a disciplined methodology and set of tools to bring high quality to product development. It begins by conducting a gap analysis of your entire product development system. This analysis finds the gaps in your processes that are negatively affecting new product performance. It also addresses a highly significant factor, the voice of the customer (VOC), as noted earlier in the quality function deployment (QFD) discussions in Chapters 2 and 4. Every new product decision must be driven by the VOC. Otherwise, what basis is there for introducing it? By learning how to identify that voice and respond to it, the designer is in a far better position to deliver a new product or service that the customer actually wants.

7.2 METHODOLOGIES

Once the gap analysis is completed and the VOC defined, the DFSS applies its own version of the Six Sigma DMAIC methodology. The steps in the DFSS methodology, known as DMADV, include the following:

- Define
- Measure
- Analyze
- Design
- Verify

The *define* step determines the project goals and the requirements of both internal and external customers. The *measure* step assesses customer needs and specifications. The *analyze* step examines process options to meet customer requirements. The *design* step develops the process to meet the customer requirements. The *verify* step checks the design to ensure that it meets customer requirements.

There are other methodologies for DFSS that have been used, including the following:

- DMADOV
- IDEAS
- IDOV
- DMEDI
- DCCDI

DMADOV is a slight modification of the DMADV methodology mentioned prior. The addition to DMADV is the *optimize* step, where the design is optimized.

IDEAS is a methodology with the following steps:

- Identify
- Design
- Evaluate
- Affirm
- Scale up

IDOV is a well-known design methodology, especially in the manufacturing world. The *identify* step identifies the customer and the critical-to-quality specifications. The *design* step

translates the customer specifications into functional requirements (FRs) and into solution alternatives. A selection process brings the list of solutions down to the "best" solution. The *optimize* step uses advanced statistical tools and modeling to predict and optimize the design and performance. The *validate* step ensures that the design that was developed will meet the customer specifications.

DMEDI is a methodology with the following steps:

- Define
- Measure
- Explore
- Develop
- Implement

DCCDI is a methodology that is fairly new. The *define* step defines the project goals. The *customer* step ensures that the analysis of the potential customer and their requirements is complete. The *concept* step is where ideas are developed, reviewed, and selected. The *design* step is performed to meet the customer and business specifications. The *implementation* step is completed to develop and commercialize the product or service.

7.3 STRUCTURE

The DFSS approach can utilize any of the many possible methodologies. The fact is that all of these methodologies use the same advanced design tools, such as QFD, Failure Modes and Effects Analysis, benchmarking, design of experiments, simulation, Robust Design, and so forth. Each methodology primarily differs in the name of each phase and the number of phases.

DFSS packages methods and tools in a framework that promotes cultural change under a recognized brand name that helps overcome an initial resistance to change. It is most useful if it generates permanent behavior changes that outlast its own life as a brand. Given that the DFSS toolset is not substantially new, the rationale for DFSS should not focus on tools. Over time, DFSS should emerge as a scientific approach to product development that leverages the Six Sigma culture. It will become a means to reinstill rigorous deductive and inductive reasoning in product development processes. It requires the following:

- Identifying customer desires
- Developing validated transfer functions that describe product performance through objective measures
- Correlating these objective measures to customer desires
- Effectively assessing the capability to meet those desires well before product launch
- Applying transfer function knowledge to optimize designs to satisfy customer desires and avoid failure modes

Six Sigma culture aids implementation of these steps by providing the following:

- A cross-company common language for problem resolution and prevention
- A mind-set that demands the use of valid data in decision making
- An expectation across the organization that results should be measurable
- A disciplined project management system to help achieve timely results

None of the elements of this approach is revolutionary, but together, they provide a template for success.

7.4 DESIGN FOR SIX SIGMA TOOLS

The use of Six Sigma tools and techniques should be introduced in a well-thought-out manner at various phases of the project. Tools that should be considered during a product development process include the following:

- Robust Design
- QFD
- Design Failure Modes and Effects Analysis
- Axiomatic Design

7.4.1 Robust Design

The Robust Design method, also called the Taguchi Method, pioneered by Dr. Genichi Taguchi, greatly improves engineering productivity. By consciously considering the noise factors (environmental variation during the product's usage, manufacturing variation, and component deterioration) and the cost of failure in the field, the Robust Design method helps ensure customer satisfaction. Robust Design focuses on improving the fundamental function of the product or process, thus facilitating flexible designs and concurrent engineering. Indeed, it is the most powerful method available to reduce product cost, improve quality, and simultaneously reduce development interval.

7.4.1.1 Why Use the Robust Design Methodology?

Over the last 5 years, many leading companies have invested heavily in the Six Sigma approach aimed at reducing waste during manufacturing and operations. These efforts have had great impact on the cost structure and, hence, on the bottom line of those companies. Many of them have reached the maximum potential of the traditional Six Sigma approach. What would be the engine for the next wave of productivity improvement?

Brenda Reichelderfer of ITT Industries reported on their benchmarking survey of many leading companies, "Design directly influences more than 70% of the product life cycle cost; companies with high product development effectiveness have earnings three times the average earnings; and companies with high product development effectiveness have revenue growth two times the average revenue growth." She also observed, "40% of product development costs are wasted!" These and similar observations by other leading companies are compelling them to adopt improved product development processes under the banner DFSS. The DFSS approach is focused on (1) increasing engineering productivity so that new products can be developed rapidly and at low cost and (2) value-based management.

The Robust Design method is central to improving engineering productivity. Pioneered by Dr. Genichi Taguchi after the end of the Second World War, the method has evolved over the last five decades. Many companies around the world have saved hundreds of millions of dollars by using the method in diverse industries: automobiles, xerography, telecommunications, electronics, software, and so forth.

7.4.1.2 Typical Problems Addressed by Robust Design

A team of engineers was working on the design of a radio receiver for ground-to-aircraft communication requiring high reliability, that is, low bit error rate, for data transmission. On the one hand, building a series of prototypes to sequentially eliminate problems would be forbiddingly expensive. On the other hand, a computer simulation effort for evaluating a single design was also time consuming and expensive. Then, how can one speed up development and yet assure reliability?

In another project, a manufacturer had introduced a high-speed copy machine to the field only to find that the paper feeder jammed almost 10 times more frequently than what was planned. The traditional method for evaluating the reliability of a single new design idea used to take several weeks. How can the company conduct the needed research in a short time and come up with a design that would not embarrass the company again in the field? The Robust Design method has helped reduce the development time and cost by a factor of two or better in many such problems.

In general, engineering decisions involved in product/system development can be classified into two categories:

- Error-free implementation of the past collective knowledge and experience
- Generation of new design information, often for improving product quality/reliability, performance, and cost

While Computer-Aided Design (CAD)/Computer-Aided Engineering (CAE) tools are effective for implementing past knowledge, the Robust Design method greatly improves productivity in generation of new knowledge by acting as an amplifier of engineering skills. With Robust Design, a company can rapidly achieve the full technological potential of their design ideas and achieve higher profits.

7.4.1.3 Robustness Strategy

Variation reduction is universally recognized as a key to reliability and productivity improvement. There are many approaches to reducing the variability, each one having its place in the product development cycle. By addressing variation reduction at a particular stage in a product's life cycle, one can prevent failures in the downstream stages. The Six Sigma approach has made tremendous gains in cost reduction by finding problems that occur in manufacturing or white-collar operations and fixing the immediate causes. The robustness strategy is to prevent problems through optimizing product designs and manufacturing process designs.

The manufacturer of a differential op-amplifier used in coin telephones faced the problem of excessive offset voltage due to manufacturing variability. High offset voltage caused poor voice quality, especially for phones further away from the central office. So, how to minimize field problems and associated cost? There are many approaches:

- Compensate the customers for their losses.
- Screen out circuits having large offset voltage at the end of the production line.
- Institute tighter tolerances through process control on the manufacturing line.
- Change the nominal values of critical circuit parameters such that the circuit's function becomes insensitive to the cause, namely, manufacturing variation.

The approach is the robustness strategy. As one moves from approach 1 to 4, one progressively moves upstream in the product delivery cycle and also becomes more efficient in cost control. Hence, it is preferable to address the problem as far upstream as possible. The robustness strategy provides the crucial methodology for systematically arriving at solutions that make designs less sensitive to various causes of variation. It can be used for optimizing product design as well as for manufacturing process design.

The robustness strategy uses five primary tools:

1. A P-Diagram is used to classify the variables associated with the product into noise, control, signal (input), and response (output) factors.
2. Ideal function is used to mathematically specify the ideal form of the signal–response relationship as embodied by the design concept for making the higher-level system work perfectly.

3. Quadratic loss function (also known as quality loss function) is used to quantify the loss incurred by the user due to deviation from target performance.
4. Signal-to-noise (S/N) ratio is used for predicting the field quality through laboratory experiments.
5. Orthogonal arrays are used for gathering dependable information about control factors (design parameters [DPs]) with a small number of experiments.

7.4.1.3.1 P-Diagram

A P-Diagram is a must for every development project. It is a way of succinctly defining the development scope. It is discussed in detail in Section 7.4.3.2.

7.4.1.4 Quality Measurement

In quality improvement and design optimization, the metric plays a crucial role. Unfortunately, a single metric does not serve all stages of product delivery. It is common to use the fraction of products outside the specified limits as the measure of quality. Though a good measure of the loss is due to scrap, it miserably fails as a predictor of customer satisfaction. The quality loss function serves that purpose very well.

Let us define the following variables:

m: target value for a critical product characteristic
+/− Δ_0: allowed deviation from the target
A_0: loss due to a defective product

Then the quality loss, L, suffered by an average customer due to a product with y as value of the characteristic is given by the following equation:

$$L = k * (y - m)^2$$

where

$$k = \left(A_0/\Delta_0^2\right)$$

If the output of the factory has distribution of the critical characteristic with mean μ and variance σ^2, then the average quality loss per unit of the product is given by

$$Q = k\ \{(\mu - m)^2 + \sigma^2\}$$

7.4.1.5 Signal-to-Noise Ratios

The product/process/system design phase involves deciding the best values/levels for the control factors. The S/N ratio is an ideal metric for that purpose. The equation for average quality loss, Q, says that the customer's average quality loss depends on the deviation of the mean from the target and also on the variance. An important class of design optimization problems requires minimization of the variance while keeping the mean on target.

Between the mean and standard deviation, it is typically easy to adjust the mean on target, but reducing the variance is difficult. Therefore, the designer should minimize the variance first and then adjust the mean on target. Among the available control factors, most of them should be used to reduce variance. Only one or two control factors are adequate for adjusting the mean on target.

The design optimization problem can be solved in two steps:

1. Maximize the S/N ratio, η, defined as

$$\eta = 10 \log_{10} (\eta^{2\sim}/\sigma^2).$$

This is the step of variance reduction.

2. Adjust the mean on target using a control factor that has no effect on *h*. Such a factor is called a scaling factor. This is the step of adjusting the mean on target.

One typically looks for one scaling factor to adjust the mean on target during design and another for adjusting the mean to compensate for process variation during manufacturing.

7.4.1.5.1 Static versus Dynamic S/N Ratios

In some engineering problems, the signal factor is absent, or it takes a fixed value. These problems are called static problems, and the corresponding S/N ratios are called static S/N ratios. The S/N ratio described in the preceding section is a static S/N ratio.

In other problems, the signal and response must follow a function called the ideal function. For example, in a cooling system, the response (room temperature) and signal (set point) must follow a linear relationship. Such problems are called dynamic problems, and the corresponding S/N ratios are called dynamic S/N ratios. Dynamic S/N ratios are very useful for technology development, which is the process of generating flexible solutions that can be used in many products.

7.4.1.5.2 Steps in Robust Parameter Design

Robust Parameter design has four main steps:

- Problem formulation:
  This step consists of identifying the main function, developing the P-Diagram, defining the ideal function and S/N ratio, and planning the experiments. The experiments involve changing the control, noise, and signal factors systematically using orthogonal arrays.
- Data collection/simulation:
  The experiments may be conducted in hardware or through simulation. It is not necessary to have a full-scale model of the product for the purpose of experimentation. It is sufficient and more desirable to have an essential model of the product that adequately captures the design concept. Thus, the experiments can be done more economically.
- Factor effects analysis:
  The effects of the control factors are calculated in this step, and the results are analyzed to select optimum setting of the control factors.
- Prediction/confirmation:
  In order to validate the optimum conditions, we predict the performance of the product design under baseline and optimum settings of the control factors. Then we perform confirmation experiments under these conditions and compare the results with the predictions. If the results of confirmation experiments agree with the predictions, then we implement the results. Otherwise, the previous steps must be iterated.

7.4.2 Quality Function Deployment

QFD was discussed in Chapters 2 and 4.

7.4.3 Robust Design Failure Mode and Effects Analysis

Failure mode and effects analysis (FMEA) is a methodology that has been used in the medical industry for many years. It is usually developed early in the product development cycle, in conjunction with a risk analysis. Risk, by definition, is the probable rate of occurrence of a hazard causing harm. Risk can be associated with device failure and also can be present in a normally operating device. The FMEA is an enhancement to the risk analysis by analyzing the potential failure down to the component level. Robust Design FMEA (DFMEA), the subject of this section, is an enhancement to the normal FMEA by anticipating safety and reliability failure modes through use of the parameter diagram (P-Diagram).

Given the fact that product design responsibility starts at the concept phase and ends when the product is obsolete, special emphases should be implemented to achieve design reliability and robustness. Robust DFMEA fits very well into this methodology. It is an invaluable tool to shorten product development times.

Robust DFMEA fits very well into the concept of concurrent engineering. It necessitates a close and continuous working relationship among design, manufacturing, service, suppliers, and customers. Robust DFMEA is best generated for the system level and used to derive through analysis the system's key subsystems and key components. Robust DFMEA preparation should incorporate inputs from a cross-functional team with expertise in design, human factors, manufacturing, testing, service, quality, reliability, clinical, regulatory, supplier, or other fields, as appropriate.

The Robust DFMEA is an integral part of the Robust Design Methodology (RDM) currently being used in Europe and is an essential tool of the DFSS process. Robust DFMEA should be generated to analyze device design through a comprehensive and structured approach using the concept of a P-Diagram. Robust DFMEA takes the failure mode analysis into a structural five-dimensional failure-cause brainstorming approach, including the following:

- *Total design and manufacturing variation*: design variability refers to the ability of the design to allow a misuse (i.e., design symmetry, can be installed upside down). Manufacturing variability refers to the special design characteristics that are sensitive to variation in manufacturing/assembly processes.
- *Changes over time*: refers to changes over time in dimensions or strength such as wear-out or degradation.
- *Customer usage*: refers to customer misuse and abuse of the product.
- *External environment*: refers to external environmental conditions.
- *System interaction*: refers to the interaction of the various subsystems and components.

7.4.3.1 Benefits of a Robust DFMEA

There are many benefits when using the Robust DFMEA, including the following:

1. Improved design reliability through a detailed analysis of system, subsystems, and components
2. Traceability back to customer needs (VOC) for validation
3. Ability to recognize and evaluate potential design failure modes and their effects
4. Ability to recognize and evaluate potential special design characteristics
5. Assurance of the implementation of proper mitigation, before the event action, to improve product reliability and robustness
6. Improvement or modification of design verification/validation planning
7. Analysis of interactions among various subsystems/components as well as interfaces to external systems
8. Analysis of all interfaces and interactions with the customer and environment
9. Definition of all stresses needed for testing

7.4.3.2 The Parameter Diagram

The parameter diagram (P-Diagram) (Figure 7.1) is a block diagram used to facilitate the understanding of Robust Design as a concept. The P-Diagram shows factors that affect a product. It models the product as a box affected by three types of parameters or factors that affect the response of the product, that is, how the product performs its intended function:

- Signal factors
- Noise factors
- Control factors

Two types of factors are controllable, whereas noise factors are uncontrollable in natural conditions of use.

- Signal factors: set by the user at a level that corresponds to the desired response
- Control factors: set by the designer

There are five elements to every P-Diagram:

1. *Inputs*: any or all of the energy, material, and information that the product requires to deliver the desirable or undesirable output.
2. *Ideal functions*: also called desirable output, which is referred to as the physical and performance requirements of an item that are used as a basis for design. Those requirements are stated in engineering terms that are unambiguous, complete, verifiable, and not in conflict with one another.
3. *Error states*: also called undesirable output or failure modes, which are referred to as the ways in which the product may fail to meet the ideal function. Error states occur in one or all of the following four states:
   a. No function
   b. Over/under/degraded function
   c. Intermittent function
   d. Unintended function
4. *Noise factors*: also called potential cause/mechanism of failure. Noise factors are the source of variation that can cause the error states/failure modes to occur. Noise factors are categorized into five categories. Any or all of the five categories mentioned may cause the error states/failure modes to occur:

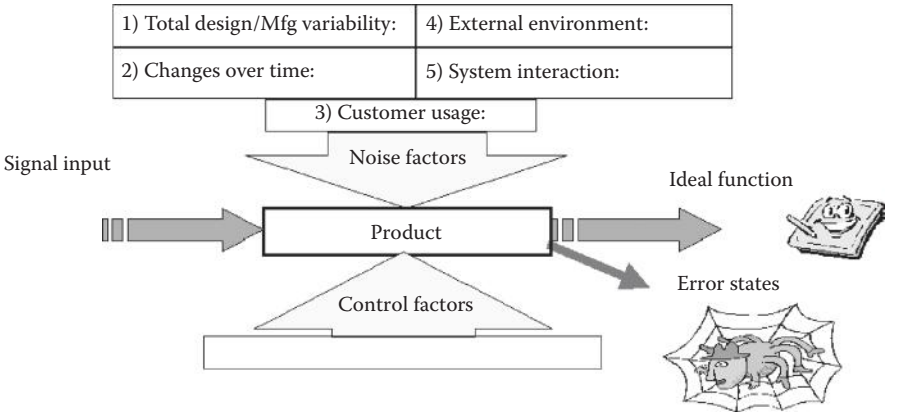

FIGURE 7.1 Parameter diagram.

Noise 1: Total design/manufacturing variability
- Design variability refers to the ability of the design to allow a misuse (i.e., design symmetry, can be installed upside down).
- Manufacturing variability refers to the key design characteristics that are sensitive to variation in manufacturing.

Noise 2: Changes over time
These are the changes over time in dimensions or strength such as wear-out or degradation.

Noise 3: Customer usage
It is customer misuse and abuse of the product.

Noise 4: External environment
It is the external environmental conditions.

Noise 5: System interaction
It is the interaction of the various subsystems and components

5. *Control factors*: the DPs used to optimize performance in the presence of noise factors.

7.4.3.3 Performing a Robust DFMEA

The DFMEA form is illustrated in Figure 7.2. The form contains the following sections:

- Number (no.):
  Enter ideal function number, start with ideal function number 1.
- Item/function:
  Enter the name of the product being analyzed. Use the nomenclature and show the design level as indicated on the engineering drawing/specification. Robust DFMEA is best generated in the following order system: key subsystems and then key components. Product under Analysis in the P-Diagram corresponds to Item in Item/Function column.

  Enter, as concisely as possible, the function of the product being analyzed to meet the design intent. If the system has more than one function, list all the functions separately. Ideal Functions in the P-Diagram corresponds to Function in Item/Function column.

Potential failure mode and effects analysis in design

(Robust design FMEA)

Project number: Product number: Page_of_

Project name: Product name: FMEA number:

Rev:

												Action results			
No.	Item/ function	Potential failure mode	Potential effect(s) of failure	SEV	Potential cause(s)/ mechanisms of failure	OCC	CLASS	Current mitigations	Verification	DET	Recommended actions	SEV	OCC	DET	CLASS
1	*Ideal functions*	*Error states*			*Noise factors*										
2															
3															

FIGURE 7.2 DFMEA diagram.

- Potential failure mode:
  List each potential failure mode for the particular product function. A recommended starting point is a review of product quality history, complaint reports, and group brainstorming. Remember that a hierarchical relationship exists between the components, subsystems, and system levels.
- Potential effect(s) of failure:
  Potential effects of failure are defined as the effects of the failure mode on the function, as perceived by the customer. Describe the effects of the failure in terms of what the customer might notice or experience, remembering that the customer may be an internal customer as well as the ultimate end user. State clearly if the function could impact safety or noncompliance to regulations. Remember that a hierarchical relationship exists between the components, subsystems, and system levels.
- Severity (S):
  Severity is an assessment of the seriousness of the effect of the potential failure mode to customer if it occurs. Severity is rated and recorded for the worst-case scenario potential effect. To ensure continuity, the Robust DFMEA team should use a consistent severity ranking system.
- Potential cause(s)/mechanism(s) of failure:
  Causes are the source of variation that causes the failure modes/error states to occur. Noise factors in the P-Diagram correspond to potential cause(s)/mechanism of failure column.
- Occurrence (O):
  Occurrence is the likelihood that a specific cause/noise factor will occur and cause the potential failure during the design life. The likelihood of occurrence ranking number has a meaning rather than a value. The following are some guidelines for defining an occurrence value:
  - What is the field experience with similar components, subsystems, or system?
  - Is it carryover or similar to a previous level component, subsystem, or system?
  - How significant are the changes from a previous level component, subsystem, or system?
  - Is it radically different from a previous level design?
  - Is it completely new?
  - Has its application/use changed?
  - What are the environmental changes?
  - Has any analysis (e.g., simulation) been used to estimate the expected comparable occurrence rate?
  - Have prevention mitigations been put in place?

  To ensure continuity, the Robust DFMEA team should use a consistent occurrence ranking system.
- Classification:
  This column may be used to classify any special product characteristics (safety and key design characteristics) for components, subsystems, and system that require mitigations. This column may also be used to highlight high-priority failure modes for assessment.
  The classification codes are illustrated in Figure 7.3.
- Current mitigations:
  Current mitigations are the activities that will assure the design adequacy for the failure mode *and/or* cause under consideration. Those activities will prevent the cause/mechanism or failure mode/effect from occurring, or reduce the rate of occurrence, such as the following:
  - Proven modeling/simulation (e.g., finite element analysis)
  - Tolerance stack-up study (e.g., geometric dimensional tolerance)
  - Material compatibility study (e.g., thermal expansion, corrosion)

Classification		
Code	To indicate	Criteria
SC	A potential safety characteristic	Severity = 5 and occurrence = 2 to 5
KC	A potential key design characteristic	Severity = 4 and occurrence = 3 to 5 Severity = 3 and occurrence = 3 to 5 Severity = 2 and occurrence = 4 to 5
AO	Action is optional	Not SC nor KC

		Severity				
		None	Low	Moderate	High	Very high
Occurrence	Sev. / Occ.	1	2	3	4	5
Remote: Failure is unlikely, improbable	1	AO	AO	AO	AO	AO
Low: Relatively few failures	2	AO	AO	AO	AO	SC
Moderate: Occasional failures	3	AO	AO	KC	KC	SC
High: Repeated/frequent failures	4	AO	KC	KC	KC	SC
Very high: Failure is almost inevitable, frequent, persistent failures	5	AO	KC	KC	KC	SC

FIGURE 7.3 Classification codes for DFMEA.

- Subjective design and manufacturing reviews
- Redundancy
- Labeling
- Design of experiment studies
- Parameter design studies
- Tolerance design studies

- Verification:
  Verify the design adequacy against cause/mechanism of failure or verify the design adequacy against failure mode, either by analytical or physical methods, such as the following:
  - Tests on preproduction samples or prototype samples
  - Analytical tests
  - Design verification plan tests

  Manufacturing tests or inspections conducted as part of the manufacturing and/or assembly process *are not* acceptable verification in the design phase.
- Detection (D):
  Detection is the ability (detection likelihood) of the *current mitigations/verification* to detect a potential cause/mechanism or failure mode and lead to corrective actions. Timeliness of current mitigations and verification application such as early in the design concept stage or just prior to release for production plays a major role in ranking the detection level. To ensure continuity, the Robust DFMEA team should use a consistent detection ranking system.

Code	To indicate	Criteria	Additional mitigation and/or recommended actions
SC	A potential safety characteristic	Severity = 5 and occurrence = 2 to 5	Risk must be mitigated and all current mitigation must be traced back to requirement. All recommended actions must be tracked via issues tracking system until occurrence brought to less or equal to 1 and detection brought to less or equal to 2.
KC	A potential key design characteristic	Severity = 4 and occurrence = 3 to 5	All current mitigations must be tracked back to requirement. All recommended actions must be tracked via issues tracking system until occurrence brought to less or equal to 2 and detection brought to less or equal to 3.
		Severity = 3 and occurrence = 3 to 5	All current mitigations must be tracked back to requirement. All recommended actions must be tracked via issues tracking system until occurrence brought to less or equal to 2 and detection brought to less or equal to 3.
		Severity = 2 and occurrence = 4 to 5	All current mitigations must be tracked back to requirement. All recommended actions must be tracked via issues tracking system until occurrence brought to less or equal to 3 and detection brought to less or equal to 3.
AO	Action optional	Not SC nor KC	Project team decides actions required.

FIGURE 7.4 Recommended actions for DFMEA.

- Recommended actions:
  The intent of recommended actions is to reduce any one or all of the severity, occurrence, and detection rankings. Only a design revision/technology change can bring a reduction in the severity ranking. Occurrence reduction can be achieved by removing or controlling the cause/mechanism of the failure mode, whereas detection reduction can be achieved by increasing the design validation/verification actions. Additional mitigations and/or recommended actions shall be implemented, as illustrated in Figure 7.4. If no actions are recommended for a specific cause, indicate this by entering "NONE" or "None at this time" in this column.
- Action results:
  Estimate and record the resulting severity, occurrence, and detection rankings and also assess classification. If no actions result, indicate this by entering "NR" in the severity, occurrence, and detection columns.

7.4.3.4 Conclusion

As a result of performing the step-by-step Robust DFMEA, one should be able to define the special design characteristics (safety and reliability product characteristics) that contribute directly to a failure mode/error state of the medical device under analysis.

Special design characteristics (safety and reliability product characteristics) defined for the product under analysis are dependent on the Robust DFMEA scope and boundary, when performed on a system, a subsystem, or a component. For example, at a system level, Robust DFMEA system-level characteristics are defined; at a subsystem level, Robust DFMEA subsystem-level characteristics are defined; and at a component level, Robust DFMEA component-level characteristics are defined.

In many cases, a system contains purchased subsystems and/or components. Robust DFMEA is capable of defining all appropriate safety and reliability product characteristics that need to reach agreement with the purchased subsystems and/or components suppliers.

Adding to all that, all safety and reliability product characteristics that are sensitive to the manufacturing process defined in the Robust DFMEA (designed in-house or purchased subsystems and components) need to derive the process FMEAs and control plans in order to achieve product reliability and robustness.

7.4.4 Axiomatic Design

Axiomatic design, a theory and methodology developed at the Massachusetts Institute of Technology (MIT; Cambridge, MA) 20 years ago, helps designers focus on the problems in bad designs. Says the theory's creator, Professor Nam Suh, "The goal of axiomatic design is to make human designers more creative, reduce the random search process, minimize the iterative trial-and-error process, and determine the best design among those proposed."

And this applies to designing all sorts of things: software, business processes, manufacturing systems, work flows, and so forth. What's more, it can be used for diagnosing and improving existing designs.

7.4.4.1 What Is Axiomatic Design?

While *MIT* and *axiomatic* might suggest some lofty academic theory, axiomatic design is well grounded in reality. It is a systematic, scientific approach to design. It guides designers through the process of first breaking up customer needs into FRs, then breaking up these requirements into DPs, and then finally figuring out a process to produce those DPs. In MIT-speak, axiomatic design is a decomposition process going from customer needs to FRs, to DPs, and then to process variables (PVs), thereby crossing the four domains of the design world: customer, functional, physical, and process. The fun begins in decomposing the design. A designer first "explodes" higher-level FRs into lower-level FRs, proceeding through a hierarchy of levels until a design can be implemented. At the same time, the designer "zigzags" between pairs of design domains, such as between the functional and physical domains. Ultimately, zigzagging between "what" and "how" domains reduces the design to a set of FR, DP, and PV hierarchies.

Along the way, there are these two axioms: the independence axiom and the information axiom. (From these two axioms come a bunch of theorems that tell designers "some very simple things," says Suh. "If designers remember these, then they can make enormous progress in the quality of their product design.") The first axiom says that the FRs within a good design are independent of each other. This is the goal of the whole exercise: identifying DPs so that "each FR can be satisfied without affecting the other FRs," says Suh.

The second axiom says that when two or more alternative designs satisfy the first axiom, the best design is the one with the least information. That is, when a design is good, information content is zero. (That is "information" as in the measure of one's freedom of choice, the measure of uncertainty, which is the basis of information theory.) "Designs that satisfy the independence axiom are called uncoupled or decoupled," explains Robert Powers, president of Axiomatic Design Software, Inc. (Boston, MA), developers of Acclaro, a software application that prompts designers through the axiomatic design process. "The difference is that in an uncoupled design, the DPs are totally independent; while in a decoupled design, at least one DP affects two or more FRs. As a result, the order of adjusting the DPs in a decoupled design is important."

The approach for design is to spend time up-front understanding customer expectations and delights (customer attributes) together with corporate and regulatory requirements. Then the following mappings are necessary:

- Perform QFD by mapping critical-to-satisfaction elements (CTS) to FRs
- Perform mapping of axiomatic design between the FRs and DPs
- Perform mapping of axiomatic design between the DPs and the PVs

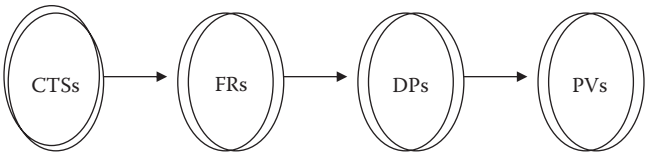

FIGURE 7.5 Axiomatic design process mapping.

The design process involves three mappings between four domains, as shown in Figure 7.5. The first mapping involves the mapping from CTS metrics to the FRs and then to DPs. The last mapping occurs between DPs and the PVs.

7.4.4.2 Mapping of Axiomatic Design

The axiomatic design method provides the process as the means to define physical and process structures. The design is first identified in terms of its FRs and then progressively detailed in terms of its lower-level FRs and DPs. Hierarchy is built by the decomposing design into a number of FRs and DPs. The principles that are used as guidance are as follows:

- Principle of independence—Maintain the independence of the FRs
- Principle of information—Minimize the information content in a design: reduce complexity

The Principle of Independence states that the optimal design maintains the independence of the FRs. An acceptable design will have the FRs and DPs related in such a way that a specific DP can be adjusted to satisfy a corresponding FR without affecting other FRs.

There are three possible mappings—uncoupled (optimal), decoupled (semi-optimal), and coupled. These mappings can be explained by use of matrices as follows:

$$\{\text{FRs}\} = [\text{A}]\{\text{DPs}\}$$

The elements of the design matrix, A, indicate the effects of changes of DPs on the FRs; as an example, consider the following design equation:

$$\begin{Bmatrix} \text{FR}_1 \\ \text{FR}_2 \\ \text{FR}_3 \end{Bmatrix} = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & 0 \\ a_{31} & 0 & a_{33} \end{bmatrix} \begin{bmatrix} \text{DP}_1 \\ \text{DP}_2 \\ \text{DP}_3 \end{bmatrix}$$

Uncoupled design is represented as follows, showing the independence of FRs:

$$\begin{Bmatrix} \text{FR}_1 \\ \text{FR}_2 \\ \text{FR}_3 \end{Bmatrix} = \begin{bmatrix} a_{11} & 0 & 0 \\ 0 & a_{22} & 0 \\ 0 & 0 & a_{33} \end{bmatrix} \begin{bmatrix} \text{DP}_1 \\ \text{DP}_2 \\ \text{DP}_3 \end{bmatrix}$$

FRs are represented as follows:

$$\text{FR}_1 = a_{11} \times \text{DP}_1$$
$$\text{FR}_2 = a_{22} \times \text{DP}_2$$
$$\text{FR}_3 = a_{33} \times \text{DP}_3$$

Decoupled design is represented as follows, showing the semi-independence of FRs:

$$\begin{Bmatrix} \mathrm{FR}_1 \\ \mathrm{FR}_2 \\ \mathrm{FR}_3 \end{Bmatrix} = \begin{bmatrix} a_{11} & 0 & 0 \\ a_{21} & a_{22} & 0 \\ a_{31} & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} \mathrm{DP}_1 \\ \mathrm{DP}_2 \\ \mathrm{DP}_3 \end{bmatrix}$$

FRs are represented as follows:

$$\mathrm{FR}_1 = a_{11} \times \mathrm{DP}_1 + 0 \times \mathrm{DP}_2 + 0 \times \mathrm{DP}_3 = a_{11} \times \mathrm{DP}_1$$
$$\mathrm{FR}_2 = a_{21} \times \mathrm{DP}_1 + a_{22} \times \mathrm{DP}_2 + 0 \times \mathrm{DP}_3 = a_{21} \times \mathrm{DP}_1 + a_{22} \times \mathrm{DP}_2$$
$$\mathrm{FR}_3 = a_{31} \times \mathrm{DP}_1 + a_{32} \times \mathrm{DP}_2 + a_{33} \times \mathrm{DP}_3$$

Coupled design is represented as follows showing the interdependencies of FRs:

$$\begin{Bmatrix} \mathrm{FR}_1 \\ \mathrm{FR}_2 \\ \mathrm{FR}_3 \end{Bmatrix} = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & 0 \\ a_{31} & 0 & a_{33} \end{bmatrix} \begin{bmatrix} \mathrm{DP}_1 \\ \mathrm{DP}_2 \\ \mathrm{DP}_3 \end{bmatrix}$$

The functional requiremements are highly interdependent, which lead to a mediocre design.

$$\mathrm{FR}_1 = a_{11} \times \mathrm{DP}_1 + 0 \times \mathrm{DP}_2 + a_{13} \times \mathrm{DP}_3 = a_{11} \times \mathrm{DP}_1 + a_{13} \times \mathrm{DP}_3$$
$$\mathrm{FR}_2 = a_{21} \times \mathrm{DP}_1 + a_{22} \times \mathrm{DP}_2 + 0 \times \mathrm{DP}_3 = a_{21} \times \mathrm{DP}_1 + a_{22} \times \mathrm{DP}_2$$
$$\mathrm{FR}_3 = a_{31} \times \mathrm{DP}_1 + a_{32} \times \mathrm{DP}_2 + a_{33} \times \mathrm{DP}_3$$

This concept is valid during mapping between DPs and PVs. In each stage, during mapping between FRs and DPs, and mapping between DPs and PVs, the principles of axiomatic design should be followed.

7.5 COMPONENT DERATING

Component failure in a given application is determined by the interaction between the strength and the stress level. When the operational stress levels of a component exceed the rated strength of the component, the failure rate increases. When the operational stress level falls below the rated strength, the failure rate decreases.

With the various ways for improving the reliability of products, derating of components is an often-used method to guarantee the good performance as well as the extended life of a product.

Derating is the practice of limiting the stresses, which may be applied to a component, to levels below the specified maximum. Derating enhances reliability through the following:

- Reducing the likelihood that marginal components will fail during the life of the system
- Reducing the effects of parameter variations
- Reducing the long-term drift in parameter values
- Providing allowance for uncertainty in stress calculations
- Providing some protection against transient stresses, such as voltage spikes

An example of component derating is the use of a 2-watt resistor in a 1-watt application. It has been shown that derating a component to 50% of its operating value generally decreases its failure rate by a factor greater than 30%. As the failure rate is decreased, the reliability is increased.

Components are derated with respect to those stresses to which the component is most sensitive. These stresses fall into two categories, operational stresses and application stresses. Operational stresses include the following:

- Temperature
- Humidity
- Atmospheric pressure

Application stresses include the following:

- Voltage
- Current
- Friction
- Vibration

These latter stresses are particularly applicable to mechanical components.

Electrical-stress usage rating values are expressed as ratios of maximum applied stress to the component's stress rating. The equation for usage ratio is as follows:

$$\text{Usage ratio} = \text{maximum applied stress/component stress rating}$$

For most electronic components, the usage ratio varies between 0.5 and 0.9.

Thermal derating is expressed as a maximum temperature value allowed or as a ratio of "actual junction temperature" to "maximum allowed junction temperature" of the device. The standard expression for temperature measurement is the Celsius scale.

Derating guidelines should be considered to minimize the degradation effect on reliability. In examining the results from a derating analysis, one often finds that a design needs less than 25 components aggressively derated to greatly improve its reliability. And, depending on the design of the product, these components often relate to an increase in capacitance voltage rating, a change of propagation speed, an increase in the wattage capacity of a selected few power resistors, and so forth.

7.6 SAFETY MARGIN

Components or assemblies will fail when the applied load exceeds the strength at the time of application. The consideration of the load should take into account combined loads, such as voltage and temperature or humidity and friction. Combined loads can have effects that are out of proportion to their separate contributions, both in terms of instantaneous effects and strength degradation effects.

Tolerancing is an essential element of assuring adequate safety margins. Tolerancing, with appropriate controls on manufacturing, provides control over the resulting strength distributions. Analysis should be based on worst-case strength or distributional analysis, rather than on an anticipated strength distribution.

Safety margin is calculated as follows:

$$\begin{aligned}\text{Safety margin} &= (\text{mean safety factor}) - 1 \\ &= (\text{Mean strength/mean stress}) - 1\end{aligned}$$

An example illustrates the concept:

A structure is required to withstand a pressure of 20,000 psi. A safety margin of 0.5 is to be designed into the device. What is the strength that must be designed in?

$$\begin{aligned}\text{Safety margin} &= (\text{strength}/\text{stress}) - 1\\ 0.5 &= (\text{strength}/20{,}000) - 1\\ 1.5 &= \text{strength}/20{,}000\\ (20{,}000 \times 1.5) &= \text{strength}\\ 30{,}000 \text{ psi} &= \text{strength}\end{aligned}$$

Most handbooks list a safety margin of 2.0 as the minimum required for high-reliability devices. In some cases, this may result in an overdesign. The safety margin must be evaluated according to device function, the importance of its application, and the safety requirements. For most medical applications, a minimum safety margin of 0.5 is adequate.

7.7 LOAD PROTECTION

Protection against extreme loads should be considered whenever practicable. In many cases, extreme loading situations can occur and must be protected against. When overload protection is provided, the reliability analysis should be performed on the basis of the maximum load that can be anticipated, bearing in mind the tolerances of the protection system.

7.8 ENVIRONMENTAL PROTECTION

Medical devices should be designed to withstand the worst-case environmental conditions in the product specification, with a safety margin included. Some typical environmental ranges that the device may experience include the following:

Operating temperature	0°C to +55°C
Storage temperature	–40°C to +65°C
Humidity	95% RH at 40°C
Mechanical vibration	5 to 300 Hz at 2 Gs
Mechanical shock	24″ to 48″ drop
Mechanical impact	10 Gs at a 50 ms pulse width
Electrostatic discharge	Up to 50,000 volts

Electromagnetic compatibility becomes an issue in an environment like an operating room. Each medical device should be protected from interference from other equipment, such as electrocautery, and should be designed to eliminate radiation to other equipment.

7.9 PRODUCT MISUSE

An area of design concern that was briefly addressed earlier in this chapter is the subject of product misuse. Whether through failure to properly read the operation manual or through improper training, medical devices are going to be misused and even abused. There are many stories of product misuse, such as the handheld monitor that was dropped into the toilet bowl, the user who used a hammer to pound a 9-volt battery into a monitor backward, or the user who spilled a can of soda on and into a device. Practically, it is impossible to make a device completely misuse-proof. But it is highly desirable to design around the ones that can be anticipated.

Some common examples of product misuse include the following:

- Excess application of cleaning solutions
- Physical abuse
- Spills
- Excess weight applied to certain parts
- Excess torque applied to controls or screws
- Improper voltages, frequencies, or pressures
- Improper or interchangeable electrical or pneumatic connections

Product misuse should be discussed with marketing to define as many possible misuse situations as can be anticipated. The designer must then design around these situations, including a safety margin, which will serve to increase the reliability of the device. Where design restrictions limit the degree of protection against misuse and abuse, the device should alarm or should malfunction in a manner that is obvious to the user.

7.10 RELIABILITY PREDICTION

Once the design has proceeded to the point where parts have been defined and a parts list developed, an initial prediction based on the parts used may be performed to produce an initial MTBF value. This value may then be compared to the original reliability goal to determine if the design will meet the intended reliability. The initial prediction is also used to highlight certain areas of the design that have a high failure rate, such as a particular component or an assembly, such as a PC board or a pneumatic circuit. The prediction is also used to form the basis for future analysis, reliability growth, and change.

Certain limitations exist with the prediction method. The first deals with the ability to accumulate data of known validity for the new application. The design may contain many new components, some of which are new to the marketplace and are not included in the standard reference handbook MIL-HDBK-217. Also, a component may be used in an application for which failure rate data have not been accumulated. In these cases, you may have to rely on vendor data or on the history of similar components in similar products.

A second limitation is the complexity of the predicting technique. It takes a long time to list each component, look up each failure rate, and then calculate the MTBF for each assembly and then the device. As the complexity of the product increases, the length of time increases. Several companies have advertised computer programs that perform the prediction. The program takes the individual components and their quantity and determines the failure rates from tables residing in the computer, which are periodically updated. No matter the effort it takes to complete, the prediction must be done to get the basis for future activities.

MIL-HDBK-217 contains two methods of doing a prediction, a parts stress analysis and a parts count analysis. The parts stress analysis requires a greater amount of detail to complete and thus is applicable at a later stage in development, when hardware testing has been completed. The parts count analysis requires a minimum of information, including the parts, quantities, quality levels, and application environment. Because it does not require operational stress levels, it can be performed early in the design phase as soon as a parts list is developed. Only the parts count method will be discussed here. Details of the parts stress analysis may be found in MIL-HDBK-217.

7.10.1 Parts Count Prediction

There are four items necessary to begin a parts count prediction:

- A schematic
- A parts list

- MIL-HDBK-217
- Marketing parameters

The marketing parameters include (1) the use rate that the number of hours the device is in operation per day, the number of days per week, and the number of weeks per year; (2) the desired MTBF goal; (3) the desired life of the device; and (4) the desired warranty cost as a percentage of sales. These parameters are used for final calculations after the MTBF has been calculated.

The first step in completing a parts count prediction is to choose the environment in which the product will be used from among the many listed in the handbook. The three most commonly experienced by medical devices in order of increasing severity are as follows:

GF Ground fixed
: Conditions less than ideal, such as installation in permanent racks, with adequate cooling air and possible installations in unheated buildings. An example would be a wall-mounted gas pressure alarm.

GB Ground benign
: Nonmobile, laboratory environment, readily accessible to maintenance. An example would be a computerized axial tomography (CAT) scan residing in one location or a monitor permanently set on a table or desk.

GM Ground mobile
: Equipment installed on wheeled or tracked vehicles. An example would be an evoked potential system that can be rolled from the operating room into a patient's room or a laboratory.

Where a question exists as to which of two environments should be chosen, select the more severe of the two. When considering the three environments, the severity of ground mobile equipment is greater than ground benign or ground fixed. The severity of ground benign is greater than ground fixed.

Once the environment is chosen, all parts, in one particular assembly, such as a PC board or a pneumatic circuit, are listed on a form, such as that shown in Figure 7.6. The form lists the type of component; the style of part, where applicable; the quantity of that component in the assembly; the failure rate for that component; and the total failure rate for the quantity of that component.

When all parts are listed on the sheet, start the process of determining the individual failure rates. The individual components are found in the appropriate tables within the parts count analysis portion of MIL-HDBK-217. The base failure rate is listed as well as the quality factor and other parameters, where necessary. The component failure rate is found by multiplying the base failure rate and the quality factor and other listed factors. This number is then listed in the individual component failure rate. This number is multiplied by the quantity included in the assembly, and the total failure rate is determined. This process continues for the remainder of the items in the assembly. When all components are determined, the total failure rates are summed to determine the failure rate for the assembly. This failure rate is listed as failures per million hours. To calculate the MTBF for the assembly, the total failure rate is divided by 1 million and the reciprocal taken. This will be the MTBF in hours.

The aforementioned process is repeated for each assembly. When completed, the total failure rates for each assembly are summed, yielding the total failure rate for the device. The MTBF for the device is calculated as it was previously, for the assembly. An example will help illustrate the method.

7.10.2 Parts Count Example

A company is developing the model 3322 Monitor. The device consists of several PC boards and a display. Reliability Engineering has the task of determining the MTBF of the device, based on the hardware components used, for comparison to the reliability goal.

Initial reliability prediction

Device_____

Subsystem_____ Date_____

Component	Style	Quantity	Individual failure rate	Total failure rate

Total failure rate_____

MTBF _____

FIGURE 7.6 Initial reliability prediction sheet.

The device will be stationary during use. Thus, the environment "GB" is chosen from MIL-HDBK-217. The parts for each PC board are listed on separate work sheets, and the failure rates calculated. Figure 7.7 shows a sample work sheet for the ADC board.

The PC board is listed in the Generic Failure Rate for Inductive and Electromechanical Parts Table of MIL-HDBK-217F (Table 7.1) under the term "PCBs." Read across the line until the column "GB" is found. The value there is 0.0054. The quality factor for the interconnects is found in the π_Q Factor for Use with Section 11-22 Devices Table (Table 7.2). Since this board is a MIL-SPEC board, the quality factor is 1. The total failure rate for the board is then the product of the initial failure rate and the quality factor.

Total failure rate = component failure rate (quality factor)

Therefore, the failure rate for the PC board is 0.0054 failures per million hours. The total failure rate for the assembly is the failure rate multiplied by the number of PC boards, in this case, one. The total failure rate is 0.0054 failures per million hours.

The resistors are type RN. The data for resistors are found in the Generic Failure Rate for Resistors Table (Table 7.3). Find style "RN" and the column "GB." The value is 0.0014. The quality value for resistors of two letter types found in this table (Table 7.4) is 10. Therefore, the failure rate for the resistors is 0.014 failures per million hours. The total failure rate for the assembly is the failure rate multiplied by the number of resistors, in this case, 30. The total failure rate for the resistors is 0.042 failures per million hours

Initial reliability prediction

Device_____3322 Monitor_____

Subsystem____ADC Board_____ Date__5/3/95_____

Component	Style	Quantity	Individual failure rate	Total failure rate
PC Board		1		
Resistors	RN	30		
Capacitors	CK	5		
Capacitors	CM	10		
Diodes	Zener	18		
Transistors	Si NPN	8		
54LS164		2		
8259		1		
54LS240		3		
54LS00		5		

Total failure rate: _____

MTBF: _____

FIGURE 7.7 Work sheet for the ADC board.

TABLE 7.1
Sample of Generic Failure Rate for Inductive and Electromechanical Parts Table

Part Type	GB
Switches	
Toggle and pushbutton	0.001
Sensitive	0.15
Thumbwheel	0.56
Circuit breakers	
Magnetic	0.06
Connectors	
Cir/rack/panel	0.011
Coaxial	0.012
PCBs	0.0054
Integrated circuit (IC) sockets	0.0019
Interconnect ASSY	0.053

TABLE 7.2
Sample of π_Q Factor for Use with Section 11-22 Devices Table

Part Type	Quality MIL-SPEC	Level Non-MIL
Inductive devices	1	10
Quartz crystals	1	2.1
Relays, solid state	1	4
Relays, time delay	1	4
Relays, mechanical	3	9
Switches, toggle and sensitive	1	20
Switches, thumbwheel	1	10
Switches, rotary wafer	1	50
Circuit breakers, thermal	1	8.4
Connectors	1	2
Interconnection assemblies	1	2

TABLE 7.3
Sample of Generic Failure Rate for Resistors Table

Part Type	GB
Composition	0.00050
Film, insulated	0.0012
Film, RN (R, C, or N)	0.0014
Film, power	0.012
Film, network	0.0023
Wirewound, accurate	0.0085
Wirewound, power	0.014

TABLE 7.4
Sample of Quality Factors for Resistors Table

Established Reliability Styles	Quality Factor
S	0.030
R	0.10
P	0.30
M	1.0
MIL-SPEC	3.0
Lower	10

Other parts have their failure rates calculated in the same manner, using the appropriate MIL-HDBK-217 tables. They are then summed to give the total failure rate for the board. The failure rate is then divided by 1 million to yield the failure rate per hour. The reciprocal of this number yields the MTBF in hours.

The total failure rate for the device is calculated by summing the individual failure rates for the subassemblies and other components. The parts previously calculated are included along with other

parts whose failure rate may be obtained from the vendor or component testing. The MTBF of the monitor is then calculated.

This value may then be compared to the reliability goal to determine if the values are comparable. It is also important to look at the individual subassemblies to determine which have the highest failure rates. The designer should then determine how the subassembly may be changed to reduce the failure rate. This may include using a component with a higher reliability or by using redundant components.

The prediction value may also be used to calculate the warranty cost for the device. To do this, several parameters for the device are necessary, including the following:

Operating time per year	2500 hours
Number of units sold per year	200 units
Selling price	$58,000
Average charge for a service call	$850

The following calculations can then be made:

$$\begin{aligned}\text{Total sales per year} &= 200 \text{ units } (\$58,000 \text{ per unit}) \\ &= \$11,600,000\end{aligned}$$

Assuming the device has an MTBF of 39,626 hours, the reliability of the device based on 2500 hours operating time per year is as follows:

$$\begin{aligned}\text{Reliability} &= \exp(-\text{use time}/\text{MTBF}) \\ &= \exp(-2500/39,626) \\ &= \exp(-0.0631) \\ &= 0.94\end{aligned}$$

This means 94% of the 200 units will survive the first year of operation without a failure, while 5%, or 12 units, will fail. Therefore, the total service charges are as follows:

$$\begin{aligned}\text{Service charge} &= 12 \text{ units } (\$850 \text{ per service cal}) \\ &= \$10,200\end{aligned}$$

The warranty cost as a percentage of sales is thus

$$\begin{aligned}\text{Warranty cost} &= (\text{service charges}/\text{total sales})\ 100 \\ &= (\$10,200/\$11,600,000)\ 100 \\ &= 0.09\% \text{ of sales}\end{aligned}$$

This value should be compared to the company standard for warranty cost.

7.10.3 Summary of Reliability Prediction

There are computer programs that will calculate a reliability prediction. The programs usually come with a database of components and failure rates. When such a program is purchased, it is essential to get periodic updates to the component database to assure that the program is using the latest failure rate values.

Experience comparing initial predictions with actual field data has shown that the parts count value is approximately 10% to 20% below the actual value calculated from field data. However, the prediction values are good indicators of trends with regard to warranty costs, serve to highlight parts of the device with high failure rates, and provide valuable information for the service department in planning the inventory of replacement parts.

Predictions can be updated after reliability testing is completed to establish a greater confidence in the calculated value.

In addition to the parts count prediction, MIL-HDBK-217 provides a second type of prediction, based on more details of how the component operates. This second type of prediction requires information such as component current, component voltage, ambient temperature, and so forth. This prediction provides a more detailed calculation for the reliability but would occur later in the development process because of the details required. The choice of the type of prediction will depend on the type of information desired and how early in the development process it is desired.

7.11 DESIGN FOR VARIATION

During design, one may need to deal with the problem of assessing the combined effects of multiple variables on a measurable output or other characteristic of a product, by means of experiments. This is not a problem that is important in all designs, particularly when there are fairly large margins between capability and required performance, for design involving negligible risk or uncertainty, or when only one or a few items are to be manufactured. However, when designs have to be optimized in relation to variations in parameter values, processes, and environmental conditions, particularly if these variations can have combined effects, it is necessary to use methods that can evaluate the effects of the simultaneous variations.

Statistical methods of experimentation have been developed that enable the effects of variation to be evaluated in these types of situation. They are applicable whenever the effects cannot be theoretically evaluated, particularly when there is a large component of random variation or interactions between variables. For multivariable problems, the methods are much more economical than traditional experiments, in which the effect of one variable is evaluated at a time. The traditional approach also does not enable interactions to be analyzed, when these are not known empirically.

7.12 DESIGN OF EXPERIMENTS

The statistical approach to design of experiments is a very elegant, economical, and powerful method for determining the s-significant effects and interactions in multivariable situations.

7.12.1 The Taguchi Method

Genichi Taguchi developed a framework for statistical design of experiments adapted to the particular requirements of engineering design. Taguchi suggested that the design process consists of three phases: system design, parameter design, and tolerance design. In the system design phase, the basic concept is decided, using theoretical knowledge and experience to calculate the basic parameter values to provide the performance required. Parameter design involves refining the values so that the performance is optimized in relation to factors and variation that are not under the effective control of the designer, so that the design is robust in relation to these. Tolerance design is the final stage, in which the effects of random variation of manufacturing processes and environments are evaluated, to determine whether the design of the product and the production processes can be further optimized, particularly in relation to cost of the product and the production processes.

Taguchi separates variables into two types. Control factors are those variables that can be practically and economically controlled, such as a controllable dimensional or electrical parameter. Noise

factors are the variables that are difficult or expensive to control in practice, though they can be controlled in an experiment, for example, ambient temperature or parameter variation with a tolerance range. The objective is then to determine the combination of control factor settings (design and process variables) that will make the product have the maximum robustness to the expected variation in the noise factors.

7.13 DESIGN CHANGES

Design changes occur throughout the design process. Often, assessing the impact of changes of all aspects of the project can be very difficult. This is particularly true for large projects involving multifunctional design teams. It is important to have the design under revision control, so that the history of changes may be tracked. To accomplish this, a design change methodology should be employed. Each change to the design should be reviewed, documented, and approved before it is implemented. A simple change form, such as that indicated in Figure 7.8, can be used. This type of form limits the number of reviewers but assures that the appropriate personnel on the development team are informed of the change.

The basic question for design change is when is a design put under revision control? For example, the product specification changes frequently at the beginning of the process, as will other documentation. To institute a change process too early will cause an excessive amount of documentation to

Design revision control sheet

Revision control number:_____

Subsystem:		Old revision:	
Origination date:		New revision:	
Origination site:			

Summary (additional information may be attached):

Change description:
Reason for the change:

Functional review:

Function	Signature
Project leader	
System coordinator	
Validation coordinator	

Non-approval (additional information may be attached):

Reason for non-approval:

Document information:

Effectivity date:	
Originator signature:	

FIGURE 7.8 Sample design change form.

become part of the project file. It is far better for all design activity that revision control be instituted after the initial flurry of changes has occurred. The activity, whether a specification, drawing, program, and so forth, should be fairly stable and have been reviewed at least once. This will allow for an orderly control of the design without excessive documentation.

7.14 DESIGN FOR MANUFACTURABILITY

Design for manufacturability (DFM) assures that a design can be repeatably manufactured while satisfying the requirements for quality, reliability, performance, availability, and price. One of the fundamental principles of DFM is reducing the number of parts in a product. Existing parts should be simple and add value to the product. All parts should be specified, designed, and manufactured to allow 100% usable parts to be produced. It takes a concerted effort by design, manufacturing, and vendors to achieve this goal.

DFM is desirable because it is less costly. The reduction in cost is due to the following:

- Simpler design with fewer parts
- Simple production processes
- Higher quality and reliability
- Greater ease of service

7.14.1 The DFM Process

The theme of DFM is to eliminate nonfunctional parts, such as screws or fasteners, while also reducing the number of functional parts. The remaining parts should each perform as many functions as possible. The following questions help in determining if a part is necessary:

- Must the part move relative to its mating part?
- Must the part be of a different material than its mating part or isolated from all other parts?
- Must the part be separate for disassembly or service purposes?

All fasteners are automatically considered candidates for elimination.

A process that can be expected to have a defect rate of no more that a few parts per million consists of the following:

- Identify critical characteristics.
- Determine product elements contributing to critical characteristics.
- For each identified product element, determine the step or process choice that affects or controls required performance.
- Determine a nominal value and maximum allowable tolerance for each product component and process step.
- Determine the capability for parts and process elements that control required performance.
- Assure that the capability index (Cp) is greater than or equal to 2, where

$$Cp = (\text{specification width})/\text{process capability}.$$

7.15 DESIGN FOR ASSEMBLY

Design for assembly (DFA) is a structured methodology for analyzing product concepts or existing products for simplification of the design and its assembly process. Reduction in parts and assembly operations, and individual part geometry changes to ease assembly are the primary

goals. The analysis process exposes many other life cycle, cost, and customer satisfaction issues that can then be addressed. Design and assembly process quality are significantly improved by this process.

Most textbook approaches to DFA discuss elimination of parts. While this is a very important aspect of DFA, there are also many other factors that affect product assembly. A few rules include the following.

7.15.1 Overall Design Concept

- The design should be simple with a minimum number of parts.
- Assure that the unit is lightweight.
- The system should have a unified design approach, rather than look like an accumulation of parts.
- Components should be arranged and mounted for the most economical assembly and wiring.
- Components that have a limited shelf life should be avoided.
- The use of special tools should be minimized.
- The use of wiring and harnesses to connect components should be avoided.

7.15.2 Component Mounting

- The preferred assembly direction is top-down.
- Repositioning of the unit to different orientations during assembly should be avoided.
- All functional internal components should mount to one main chassis component.
- Mating parts should be self-aligning.
- Simple, foolproof operations should be used.

7.15.3 Test Points

- Pneumatic test point shall be accessible without removal of any other module.
- Electrical test points shall include, but not be limited to, the following:
  - Reference voltages
  - Adjustments
  - Key control signals
  - Power supply voltages
- All electronic test points shall be short-circuit protected and easily accessible.

7.15.4 Stress Levels and Tolerances

- The lowest possible stress levels should be used.
- The maximum possible operating limits and mechanical tolerances should be maximized.
- Operations of known capability should be used.

7.15.5 PCBs

- Adequate clearance should be provided around circuit board mounting locations to allow for tools.
- Components should be soldered, not socketed.
- PCBs must be mechanically secured and supported.
- There must be unobstructed access to test and calibration points.
- Exposed voltages should be less than 40 volts.

7.15.6 Miscellaneous

- All air intakes should be filtered, and an indication that the filter needs to be changed should be given to the user.
- The device shall be packed in a recyclable container so as to minimize the system installation time.

7.15.7 Design for Assembly Process

- Develop a multifunctional team before the new product architecture is defined. This team should foster a creative climate that will encourage ownership of the new product's design and delivery process.
- Establish product goals through a benchmarking process or by creating a model, drawing, or conception of the product.
- Perform a DFA analysis of the product. This identifies possible candidates for elimination or redesign, as well as highlighting high-cost assembly operations.
- Segment the product architecture into manageable modules or levels of assembly.
- Apply DFA principles to these assembly modules to generate a list of possible cost opportunities.
- Apply creative tools, such as brainstorming, to enhance the emerging design and identify further design improvements.
- As a team, evaluate and select the best ideas, thus narrowing and focusing the team's goals.
- Make commodity and material selections. Start early supplier involvement to assure economical production.
- With the aid of cost models or competitive benchmarking, establish a target cost for every part in the new design.
- Start the detailed design of the emerging product. Model, test, and evaluate the new design for form, fit, and function.
- Reapply the process at the next logical point.
- Share the results.

7.16 DESIGN REVIEWS

Despite discipline, training, and care, it is inevitable that occasional oversights or errors will occur in new designs. Design reviews are held to highlight critical aspects of the design and to focus attention on possible shortfalls. Design review are held to

- Review the progress of a design
- Monitor reliability growth
- Assure all specifications are being addressed
- Peer review the design approach

The primary purpose of the design review is to make a choice among alternative design approaches. The output of the review should include an understanding of the weak areas in the design and the areas of the design in need of special attention. Topics to be covered in a design review include the following:

- Redundancy versus derating
- Redesign of weak areas versus high-reliability parts
- Review of FMEA
- Review of potential product misuse
- Review overstressed areas

The design review should follow a structured order and be well documented with topics discussed, decisions reached, and resulting action items.

There are three overall types of design reviews:

- *Informal design reviews*: To address detailed technical design and performance issues, usually for an isolated part of the product.
- *Formal design review*: To address technical performance issues for the entire product and correlate activities with the project objectives and the product specifications.
- *Program review*: To examine the project relative to budget and schedule performance, technical discoveries, or limitations. Program reviews, also known as progress (or project) reviews, are generally conducted by senior managers and do not concern themselves with technical reviews of design.

Formal design reviews are generally held according to the project plan and are convened to support major project milestones. Plenty of time should be allowed for the review meeting. People should be invited who will challenge the design, including experts. The purpose is to review theory, technical design specs, implementation, and performance to specification. The design review should be held to challenge the design, not familiarize people with it. If familiarization is needed, a separate session should be held prior to the actual review. People should be allowed to talk freely. Criticism should be expected and accepted. A dedicated person not expected to participate in the review should be asked to take the minutes.

Informal design reviews are generally not scheduled per the project plan and are convened when the need arises to address specific concerns. Generally, only local reviewers are invited. The informal reviews are used to brainstorm a particularly tough problem or to analyze alternate design approaches. These reviews are generally extremely detailed and focus on a particular subsystem, module, or component. Informal review results are usually documented in lab notebooks or supporting memos.

For all design reviews, it is optimal to assure that the design review personnel have not taken part in the actual design activity. This gives a fresh and unbiased look at the design. Some of the guidelines for design reviewers include the following:

- Design reviewers have a serious responsibility to comment on the potential outcome of the project.
- When notice of review meetings are announced, reviewers should plan ahead and take time to prepare for the reviews.
- The reviewers should assure that they understand project objectives and the product specification.
- Reviewers should attend all formally planned learning sessions.
- If possible, reviewers should submit concerns and questions to the review chair in advance of the design review meeting. The issues and concerns can be discussed in depth at the meeting.
- Reviewers should help the design review leader during the meeting by questioning the design's performance relative to the product specification, design specification, project objectives, safety, effectiveness, and reliability of the product's functioning. At this stage, being harshly, constructively, critical is being helpful.

EXERCISES

1. Use the term *reverse engineer* in a web search. Report on the variety of firms offering this service.
2. Use the term *value engineering* in a web search. How does it differ from reverse engineering?

3. Use the term *reengineering* in a web search. How does this relate to reverse engineering?
4. Perform a web search on the term *axiomatic design*. Print out and summarize an article of interest to you.

SUGGESTED READING

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8 Software Development Methods and Tools

The hardest single part of building a software system is deciding precisely what to build.

Frederick P. Brooks

Software design and implementation is a multistaged process in which system and software requirements are translated into a functional program that addresses each requirement. Good software designs are based on a combination of creativity and discipline. Creativity provides resolution to new technical hurdles and the challenges of new market and user needs. Discipline provides quality and reliability to the final product.

Software design begins with the Software Requirements Specification. The design itself is the system architecture, which addresses each of the requirements of the specification and any appropriate software standards or regulations.

The top-level design begins with the analysis of software design alternatives and their trade-offs. The overall software architecture is then established along with the design methodology to be used and the programming language to be implemented. A risk analysis is performed and then refined to assure that malfunction of any software component will not cause harm to the patient, the user, or the system. Metrics are established to check for program effectiveness and reliability. The requirements traceability matrix (RTM) is reviewed to assure that all requirements have been addressed. The software design is reviewed by peers for completeness.

The detailed design begins with modularizing the software architecture, assigning specific functionality to each component, and assuring that both internal and external interfaces are well defined. Coding style and techniques are chosen based on their proven value and the intended function and environment of the system. Peer reviews assure the completeness and effectiveness of the design. The detailed design also establishes the basis for subsequent verification and validation activity. The use of automated tools throughout the development program is an effective method for streamlining the design and development process and assists in developing the necessary documentation.

8.1 SOFTWARE DESIGN LEVELS

Software design may be divided into two distinct stages:

1. Top-level design
   - Design alternatives and trade-offs
   - Software architecture
   - Choosing a methodology
   - Structural analysis
   - Object-oriented design
   - Choosing a language
   - Software risk analysis
   - The software RTM
   - Software review

2. Detailed design
   - Design techniques
   - Performance predictability and design simulation
   - Module specification
   - Coding
   - Design support tools
   - Design as a basis for verification and validation testing

8.2 DESIGN ALTERNATIVES AND TRADE-OFFS

The determination of the design and the allocation of requirements is a very iterative process. Alternative designs are postulated that are candidates to satisfy the requirements. The determination of these designs is a fundamentally creative activity, a "cut-and-try" determination of what might work. The specific techniques used are numerous and call upon a broad range of skills. They include control theory, optimization, consideration of man–machine interface, use of modern control test equipment, queuing theory, communication and computer engineering, statistics, and other disciplines. These techniques are applied to factors such as performance, reliability, schedule, cost, maintainability, power consumption, weight, and life expectancy.

Some of the alternative designs will be quickly discarded, while others will require more careful analysis. The capabilities and quality of each design alternative is assessed using a set of design factors specific to each application and the methods of representing the system design.

Certain design alternatives will be superior in some aspects, while others will be superior in different aspects. These alternatives are "traded off," one against the other, in terms of the factors important for the system being designed. The design ensues from a series of technology decisions, which are documented with architecture diagrams that combine aspects of data and control flow. As an iterative component of making technology decisions, the functionality expressed by the data flow and control flow diagrams from system requirements analysis is allocated to the various components of the system. Although the methods for selection of specific technology components are not a part of the methodology, the consequences of the decisions are documented in internal performance requirements and timing diagrams.

Finally, all factors are taken into account, including customer desires and political issues to establish the complete system design. The product of the system design is called an architecture model. The architecture includes the components of the system, allocation of requirements, and topics such as maintenance, reliability, redundancy, and self-test.

8.3 SOFTWARE ARCHITECTURE

Software architecture is the high-level part of software design, the frame that holds the more detailed parts of the design. Typically, the architecture is described in a single document referred to as the architecture specification. The architecture must be a prerequisite to the detailed design, because the quality of the architecture determines the conceptual integrity of the system. This in turn determines the ultimate quality of the system.

A system architecture first needs an overview that describes the system in broad terms. It should also contain evidence that alternatives to the final organization have been considered and the reasons the organization used was chosen over the alternatives. The architecture should also contain the following:

- Definition of the major modules in a program. What each module does should be well defined, as well as the interface of each module.
- Description of the major files, tables, and data structures to be used. It should describe alternatives that were considered and justify the choices that were made.

- Description of specific algorithms or reference to them.
- Description of alternative algorithms that were considered and indication of the reasons that certain algorithms were chosen.
- In an object-oriented system, specification of the major objects to be implemented. It should identify the responsibilities of each major object and how the object interacts with other objects. It should include descriptions of the class hierarchies, of state transitions, and of object persistence. It should also describe other objects that were considered and give reasons for preferring the organization that was chosen.
- Description of a strategy for handling changes clearly. It should show that possible enhancements have been considered and that the enhancements most likely are also easiest to implement.
- Estimation of the amount of memory used for nominal and extreme cases.

Software architecture alludes to two important characteristics of a computer program: (1) the hierarchical structure of procedural components (modules) and (2) the structure of data. Software architecture is derived through a partitioning process that relates elements of a software solution to parts of a real-world problem implicitly defined during requirements analysis. The evolution of a software structure begins with a problem definition. The solution occurs when each part of the problem is solved by one or more software elements.

An architectural template may be developed that gives a general layout for all the architectural model diagrams to follow. This template indicates the physical perspectives that had not existed in the system requirements. Areas that may be included in the template are as follows:

- User interface processing
- Maintenance, self-test, and redundancy requirements
- Input processing
- Output processing

User interface processing is the system-to-user interface, requiring some technology-based enhancements that were omitted in the requirements model. These enhancements are based on use of available technology and on various cost, operational environment, and other criteria. The architecture should be flexible so that a new user interface can be substituted without affecting the processing and output parts of the program.

Maintenance, self-test, and redundancy processing requirements are also technology dependent. These requirements cannot be identified until an implementation technology has been selected that meets the system's reliability and performance criteria.

Input/output (I/O) is another area that deserves attention in the architecture. Input processing refers to the communications across the system's boundary that were not addressed in the system requirements and are not part of the user interface or a maintenance interface. Additional processing is added depending on technology decisions. Output processing involves the same considerations as input processing. Output processing takes the system's logical output and converts it to a physical form. The architecture should specify a look-ahead, look-behind, or just-in-time reading scheme, and it should describe the level at which I/O errors are detected.

The detailed architecture may be expressed in various forms. Examples include the following:

- Architecture context diagram: the top-level diagram for the architecture model. It contains the system's place in its environment and, in addition, the actual physical interface to the environment.
- Architecture flow diagram: the network representation of the system's physical configuration.

8.4 CHOOSING A METHODOLOGY

It seems there are about as many design methodologies as there are engineers to implement them. Typically, the methodology selection entails a prescription for the requirements analysis and design processes. Of the many popular methods, each has its own merit based on the application to which the methods are applied. The tool set and methodology selection should run hand in hand. Tools should be procured to support established or tentative design methodology and implementation plans. In some cases, tools are purchased to support a methodology already in place. In other cases, the methodology is dictated by an available tool set. Ideally, the two are selected at the same time following a thorough evaluation of need.

Selecting the right tool set and design methodology should not be based on a flashy advertisement or suggestion from an authoritative methodology guru. It is important to understand the environment in which it will be employed and the product to which it will be applied. Among other criteria, the decision should be based on the size of the project (number of requirements), type of requirements (hard or soft real-time), complexity of the end product, number of engineers, experience and skill level of the engineers, project schedules, project budget, reliability requirements, and future enhancements to the product (maintenance concerns). Weight factors should be applied to the evaluation criteria. One way or another, whether the evaluation is done in a formal or informal way, involving one or more than one person, it should be done to assure a proper fit for the organization and product.

Regardless of the approach used, the most important factor to be considered for the successful implementation of a design methodology is software development team buy-in. The software development team must possess the confidence that the approach is appropriate for the application and be willing and "excited" to tackle the project. The implementation of a design methodology takes relentless discipline. Many projects have been unsuccessful as a result of lack of commitment and faith.

The two most popular formal approaches applied to the design of medical products are object oriented analysis/design and the more traditional (top-down) structured analysis/design. There are advantages and disadvantages to each. Either approach, if done in a disciplined and systematic manner along with the electrical system design, can provide for a safe and effective product.

8.5 STRUCTURED ANALYSIS

Structured analysis is the process of examining the software requirements for the purposes of generating a structural model of the requirements. This activity focuses on data flowing through the system. In particular, data transformations are identified that occur in the process of delivering the required outputs from given inputs. A thorough structured analysis of the system will provide a complete and well-understood set of software requirements, which is highly conducive to the ensuing structured design process.

Structured design entails an abstraction of the analysis which results into a top-down, functional decomposition of the requirements. Structured design focuses on the decomposition of the operations to be performed on the data. At the onset, a series of high-level functional blocks are identified, which, in collection, address all processing expectations of the system. In a systematic manner, a hierarchy of ever smaller processing units are evolved from the high-level blocks. This iterative partitioning produces a series of small, procedural components, which, when integrated, form a system capable of satisfying all functional requirements.

Structured design is the most common approach to software design today. Design of systems from the functional decomposition perspective has been around for decades, and its approach is the most well understood and mature. Its weaknesses, however, lie in the emphasis on sequential thinking and the generation of solutions based on procedural connection among functional blocks. Most software developers will agree that this is not a natural representation of real-world objects and the relationships between them.

Although normally manageable in small- to medium-scale software systems, it is inherent that most product requirement changes result in significant design changes unless they were anticipated from the start. Certain types of changes can be very expensive to make because of their disturbance of some of the predefined high-level procedural flows. Unforeseen changes can also lead to reduced product confidence and reliability. Increased complexity often results when trying to retain harmony among existing components in the presence of new and sometimes foggy relationships.

8.6 OBJECT-ORIENTED DESIGN

The object-oriented design paradigm seeks to mimic the way that people form models of the real world. In contrast to procedural design methods, it de-emphasizes the underlying computer representation. Its major modeling concept is that of the object, which is used to symbolize real-world entities and their interactions. Objects are entities that have state and behavior. They can be implemented in computer systems as data and a set of operations defined over those data.

Although at its lowest level of design, object-oriented design resembles structured design and traditional code development; during the analysis and high-level design phases, a different mind-set surrounds the attack of the problem. Object-oriented design hinges on approaching design solutions in terms of the identification of objects, associated object attributes, and operations performed on and among the objects. This approach generates designs that map very well to "real-world" items and operations, thus leading to designs that can be easier to understand and maintain.

Object-oriented designs have been found to be a very successful approach to the design of some large, more complex systems. This has garnered the attention of software developers around the world. There are, however, two generally recognized blemishes currently associated with the approach. Developers often have difficulty agreeing on the definitions of objects and object classes. This has resulted in system designs that are not as easy to understand as expectations would have you believe. Also, an additional processing overhead is associated with the implementation of object-oriented programming languages. This inefficiency has deterred many from using the approach on embedded real-time medical systems because of the increased hardware cost incurred to deliver acceptable system performance. Still, as the price of processing power for the dollar decreases, it can be expected that object-oriented programming will increase in popularity as a viable approach to the development of high-performance, competitively priced medical products.

8.7 CHOOSING A LANGUAGE

Programming languages are the notational mechanisms used to implement software products. Features available in the implementation language exert a strong influence on the architectural structure and algorithmic details of the software. Choice of language has also been shown to have an influence on programmer productivity. Industry data have shown that programmers are more productive using a familiar language than an unfamiliar one. Programmers working with high-level languages achieve better productivity than those working with lower-level languages. Developers working in interpreted languages tend to be more productive than those working in compiled languages. In languages that are available in both interpreted and compiled forms, programs can be productively developed in the interpreted form and then released in the better-performing compiled form.

Computer languages are the malleable tools for program design and implementation alike. From one perspective, they offer representations of computer procedures that can consolidate the understanding gained from a prototyping process and then link these key requirements to machine capabilities. From another perspective, they can impose structure and clarity on the logical flow of a system with an eye toward operational efficiency and reliability. In principle, these two perspectives should converge. In actual practice, they often conflict. The problem of how to move from an initial

design through the necessary revisions to implementation is the underlying issue in the choice and use of language in medical systems.

Modern programming languages provide a variety of features to support development and maintenance of software products. These features include the following:

- Strong type checking
- Separate compilation
- Used-defined data types
- Data encapsulation
- Data abstraction

The major issue in type checking is flexibility versus security. Strongly typed languages provide maximum security, while automatic type coercion provides maximum flexibility. The modern trend is to augment strong type checking with features that increase flexibility while maintaining the security of strong type checking.

Separate compilation allows retention of program modules in a library. The modules are linked into the software system, as appropriate, by the linking loader. The distinction between independent compilation and separate compilation is that type checking across compilation–unit interfaces is performed by a separate compilation facility but not by an independent compilation facility.

User-defined data types, in conjunction with strong type checking, allow the programmer to model and segregate entities from the problem domain using a different data type for each type of problem entity.

Data encapsulation defines composite data objects in terms of the operations that can be performed on them, and the details of data representation and data manipulation are suppressed by the mechanisms. Data encapsulation differs from abstract data types in that encapsulation provides only one instance of an entity.

Data abstraction provides a powerful mechanism for writing well-structured, easily modified programs. The internal details of data representation and data manipulation can be changed at will and, provided that the interfaces of the manipulation procedures remain the same, other components of the program will be unaffected by the change, except perhaps for changes in performance characteristics and capacity limits. Using a data abstraction facility, data entities can be defined in terms of predefined types, user-defined types, and other data abstractions, thus permitting systematic development of hierarchical abstractions.

One of the most striking things about computer languages is that there are so many of them. All have struggled to keep up with the increasing individuality and complexity of modern computer systems. To be successful, a language must mediate between (1) the capabilities and limitations of the machine on which the applications run, (2) the properties of the information domain that is to be addressed, (3) the characteristics of the user, and (4) the exchange of information between machines. Ideally, every language should be a proper reflection of these four perspectives.

When choosing a language, careful evaluation is necessary for a particular program. Table 8.1 lists some languages and their suitability for various purposes. The classifications are broad, so care must be taken in their use. Among the many languages available, each has its pros and cons, depending on its specific application. Table 8.2 lists some of the pros and cons for individual languages. In addition to the pros and cons, the following language characteristics should be analyzed in making a choice:

- Clarity, simplicity, and unity of language concept
- Clarity of program syntax
- Naturalness of application
- Support for abstraction
- Ease of verification

TABLE 8.1
Language Suitability for Programming Situations

Kind of Programs	More Effective Languages	Less Effective Languages
Structured data	Ada, C/C++, Pascal	Assembler, Basic
Quick and dirty project	Basic	Ada, Assembler, Pascal
Fast execution	Assembler, C	Interpreted Languages
Mathematical calculations	Fortran	Pascal
Easy to maintain	Ada, Pascal	C, Fortran
Dynamic memory usage	C, Pascal	Basic
Limited memory environments	Assembler, Basic, C	Ada, Fortran
Real-time program	Ada, Assembler, C	Basic, Fortran
String manipulation	Basic, Pascal	C

TABLE 8.2
Pros and Cons of Software Languages

Language	Pros	Cons
Ada	Some software engineering techniques are embedded in the language. Portable, broad range of language constructs. Built-in microprocessing.	Large, overkill for many applications. Development systems are expensive to purchase. Life cycle costs are up front.
Assembler	Very fast, low-level programming when other languages are unsuitable.	High maintenance cost due to level or readability. High portability of errors, not portable, old, low-level language.
Basic	Good beginner language. Straightforward commands.	Slow, unstructured, difficult to maintain.
C	Wide usage, portable, fast, powerful. Recently became an American National Standards Institute (ANSI) standard language.	Too powerful for the inexperienced programmer.
Cobol	Good for large amounts of data, simple calculations, business record processing.	Bad for scientific applications, poor support of complex calculations, slow.
Fortran	Well suited for scientific and engineering applications.	Old technology.
Modula-2	Pascal-like yet modular.	Not widely used, no language standard, several dialects.
Pascal	Flexible data typing, structured, good beginner language.	Monolithic, confining.

- Programming environment
- Portability of programs
- Cost of use
- Familiarity of design team with the language

8.8 SOFTWARE RISK ANALYSIS

Software risk analysis techniques identify software hazards and safety-critical single- and multiple-failure sequences; determine software safety requirements, including timing requirements; and analyze and measure software for safety. While functional requirements often focus on what the system shall do, risk requirements must also include what the system shall not do—including means of eliminating and controlling system hazards and of limiting damage in case of a mishap. An

important part of the risk requirements is the specification of the ways in which the software and the system can fail safely and to what extent failure is tolerable.

Several techniques have been proposed and used for doing risk analysis, including the following:

- Software hazard analysis
- Software fault tree analysis
- Real-time logic

Software hazard analysis, like hardware hazard analysis, is the process whereby hazards are identified and categorized with respect to criticality and probability. Potential hazards that need to be considered include normal operating modes, maintenance modes, system failure or unusual incidents in the environment, and errors in human performance. Once hazards are identified, they are assigned a severity and probability. Severity involves a qualitative measure of the worst credible mishap that could result from the hazard. Probability refers to the frequency with which the hazard occurs. Once the probability and severity are determined, a control mode is established, that is, a means of reducing the probability and/or severity of the associated potential hazard. Finally, a control method or methods are selected to achieve the associated control mode.

Fault tree analysis is an analytical technique used in the risk analysis of electromechanical systems. An undesired system state is specified, and the system is analyzed in the context of its environment and operation to find credible sequences of events that can lead to the undesired state. The fault tree is a graphic model of various parallel and sequential combinations of faults or system states that will result in the occurrence of the predefined undesired event. It thus depicts the logical interrelationships of basic events that lead to the hazardous event.

Real-time logic is a process wherein the system designer first specifies a model of the system in terms of events and actions. The event–action model describes the data dependency and temporal ordering of the computational actions that must be taken in response to events in a real-time application. The model can be translated into real-time logic formulas. The formulas are transformed into predicates of Presburger arithmetic with uninterpreted integer functions. Decision procedures are then used to determine whether a given risk assertion is a theorem derivable from the system specification. If so, the system is safe with respect to the timing behavior denoted by that assertion, as long as the implementation satisfies the requirements specification. If the risk assertion is unsatisfiable with respect to the specification, then the system is inherently unsafe because successful implementation of the requirements will cause the risk assertion to be violated. Finally, if the negation of the risk assertion is satisfiable under certain conditions, then additional constraints must be imposed on the system to assure its safety.

8.9 THE REQUIREMENTS TRACEABILITY MATRIX

It is becoming more and more apparent how important thorough requirements traceability is during the design and development stages of a software product, especially in large projects with requirements numbering in the thousands or tens of thousands. Regardless of the design and implementation methodology, it is important to assure that the design is meeting its requirements during all phases of design.

To ensure that the product is designed and developed in accordance with its requirements throughout the development cycle, individual requirements should be assigned to design components. Each software requirement, as might appear in a Software Requirements Specification, for example, should be uniquely identifiable. Requirements resulting from design decisions (i.e., implementation requirements) should be uniquely identified and tracked along with product functional requirements.

This process not only assures that all functional and safety features are built into the product as specified but also drastically reduces the possibility of requirements “slipping through the cracks.”

TABLE 8.3
Requirements Traceability Matrix

Requirement	Design	Code	Unit Test	Integration Test
Accept only valid input	check_input	check_num.c	num_only.tc	whole_valid.tc
		check_char.c	char_only.tc	whole_inval.tc
		check_mixed.c	mixed.tc	
Requirement 2				

Overlooked features can be much more expensive when they become design modifications at the tail end of development.

The RTM is generally a tabular format with requirements identifiers as rows and design entities as column headings. Individual matrix cells are marked with file names or design model identifiers to denote that a requirement is satisfied within a design entity.

An RTM assures completeness and consistency with the software specification. This can be accomplished by forming a table that lists the requirements from the specification versus how each is met in each phase of the software development process. Table 8.3 is an example of an RTM.

8.10 SOFTWARE REVIEW

An integral part of all design processes is timely and well-defined reviews. Each level of design should produce design review deliverables. Software project development plans should include a list of the design phases, the expected deliverables for each phase, and a sound definition of the deliverables to be audited at each review. Reviews of all design material have several benefits. First and foremost, knowing that their work is being reviewed, authors are more compelled to elevate the quality of their work. Secondly, reviews often uncover design blind spots and alternative design approaches. Finally, the documentation generated by the reviews is used to acquire agency approvals for process and product.

Software reviews may take several different forms:

- Inspections of design and code
- Code walk-throughs
- Code reading
- Dog-and-pony shows

An inspection is a specific kind of review that has been shown to be extremely effective in detecting defects and to be relatively economical compared to testing. Inspections differ from the usual reviews in several ways:

- Checklists focus the reviewer's attention on areas that have been problems in the past.
- The emphasis is on defect detection, not correction.
- Reviewers prepare for the inspection meeting beforehand and arrive with a list of the problems they have discovered.
- Data are collected at each inspection and are fed into future inspections to improve them.

An inspection consists of several distinct stages:

- *Planning*: The moderator, after receiving the documentation, decides who will review the material and when and where the review will take place.

- *Overview*: The author describes the technical environment within which the design or code has been created.
- *Preparation*: Each reviewer works alone to become familiar with the documents.
- *Inspection meeting*: The moderator chooses someone, usually the author, to paraphrase the design or read the code. The scribe records errors as they are detected, but discussion of an error stops as soon as it is recognized as an error.
- *Inspection report*: The moderator produces an inspection report that lists each defect, including its type and severity.
- *Rework*: The moderator assigns defects to someone, usually the author, for repair. The assignee(s) resolves each defect on the list.
- *Follow-up*: The moderator is responsible for seeing that all rework assigned during the inspection is carried out.

The general experience with inspections has been that the combination of design and code inspections usually removes 60% to 90% of the defects in a product. Inspections identify error-prone routines early, and reports indicate that they result in 30% fewer defects per 1000 lines of code than walk-throughs do. The inspection process is systematic because of its standard checklists and standard roles. It is also self-optimizing because it uses a formal feedback loop to improve the checklists and to monitor preparation and inspection rates.

A walk-through usually involves two or more people discussing a design or code. It might be as informal as an impromptu bull session around a whiteboard; it might be as formal as a scheduled meeting with overhead transparencies and a formal report sent to management. Some of the characteristics of a walk-through include the following:

- The walk-through is usually hosted and moderated by the author of the design or code under review.
- The purpose of the walk-through is to improve the technical quality of a program rather than to assess it.
- All participants prepare for the walk-through by reading design or code documents and looking for areas of concern.
- The emphasis is on error detection, not correction.
- The walk-through concept is flexible and can be adapted to the specific needs of the organization using it.

Used intelligently, a walk-through can produce results similar to those of an inspection—that is, it can typically find between 30% and 70% of the errors in a program. Walk-throughs have been shown to be marginally less effective than inspections but, in some circumstances, can be preferable. Table 8.4 is a comparison of inspections and walk-throughs.

Code reading is an alternative to inspections and walk-throughs. In code reading, you read source code and look for errors. You also comment on qualitative aspects of the code, such as its design, style, readability, maintainability, and efficiency.

A code reading usually involves two or more people reading code independently and then meeting with the author of the code to discuss it. To prepare for a meeting, the author hands out source listings to the code readers. Two or more people read the code independently. When the reviewers have finished reading the code, the code-reading meeting is hosted by the author of the code and focuses on problems discovered by the reviewers. Finally, the author of the code fixes the problems identified by the reviewers.

The difference between code reading on the one hand and inspections and walk-throughs on the other is that code reading focuses more on individual review of the code than on the meeting. The result is that each reviewer's time is focused on finding problems in the code. Less time is spent in meetings.

TABLE 8.4
Comparison of Inspections and Walk-Throughs

Properties	Inspections	Walk-Throughs
Formal moderator training	Yes	No
Distinct participant roles	Yes	No
Who "drives" the inspection or walk-through	Moderator	Author
Checklists for finding errors	Yes	No
Focused review effort—looks for the most frequently found kinds of errors	Yes	No
Formal follow-up to reduce bad fixes	Yes	No
Fewer future errors because of detailed error feedback to individual programmers	Yes	Incidental
Improved inspection efficiency from analysis of results	Yes	No
Analysis of data leading to detection of problems in the process, which in turn leads to improvements in the process	Yes	No

Dog-and-pony shows are reviews in which a software product is demonstrated to a customer. The purpose of the review is to demonstrate to the customer that the project is proceeding, so it is a management review rather than a technical review. They should not be relied on to improve the technical quality of a program. Technical improvement comes from inspections, walk-throughs, and code reading.

The software development process now moves into the detailed design stage.

8.11 DESIGN TECHNIQUES

Good software design practice is more than a matter of applying one of the latest design methodologies. Thorough requirement generation, requirements tracking, requirements analysis, performance predictability, system simulation, and uniform design reviewing are all activities that contribute to the development of safe and effective software designs.

8.12 PERFORMANCE PREDICTABILITY AND DESIGN SIMULATION

A key activity of design often overlooked by some software developers is the effort to predict the real-time performance of a system. During the integration phase, software designers often spend countless hours trying to finely tune a system that had bottlenecks "designed in." Execution estimates for the system interfaces, response times for external devices, algorithm execution times, operating system context switch time, and I/O device access times in the forefront of the design process provide essential input into software design specifications.

For single processor designs, mathematical modeling techniques such as rate monotonic analysis (RMA) should be applied to assure that all required operations of that processing unit can be performed in the expected time period. System designers often fall into the trap of selecting processors before the software design has been considered, only to experience major disappointment and "finger pointing" when the product is released. It is imperative to a successful project that the processor selection come after a processor loading study is complete.

In a multiprocessor application, up-front system performance analysis is equally important. System anomalies can be very difficult to diagnose and resolve in multiprocessor systems with heavy interprocessor communications and functional expectations. Performance shortcomings that appear to be the fault of one processor are often the result of a landslide of smaller inadequacies from one or more of the other processors or subsystems. Person-years of integration phase defect resolution can be eliminated by front-end system design analysis and/or design simulation. Commercial tools are readily available to help perform network and multiprocessor communications analysis

and execution simulation. Considering the pyramid of effort needed in software design, defect correction in the forefront of design yields enormous cost savings and increased reliability in the end.

8.13 MODULE SPECIFICATIONS

The lowest level of software design is typically referred to as module specifications or "mspecs." A complete set of mspecs details the actual definitions for the routine names, interfaces (inputs and outputs) of the routines, resident data structures, and "pseudocode" for each routine. The pseudocode for each routine should explicitly detail the flow of logic through the routine, including the lowest level algorithms, decision branches, and usage of data structures. Module specifications are generated for both structured designs and object-oriented designs and usually become part of the documentation associated with the source code as routine header information. Accurate mspecs are an essential part of all software design, regardless of tool set and methodology selection. This is especially true when the mspec designer and the coder are not the same person.

8.14 CODING

For many years, the term "software development" was synonymous with coding. Today, for many software development groups, coding is now one of the shortest phases of software development. In fact, in some cases, although very rare in a world of real-time embedded software development, coding is actually done automatically from higher-level design (mspecs) documentation by automated tools called "code generators."

With or without automatic code generators, the effectiveness of the coding stage is dependent on the quality and completeness of the design documentation generated in the immediately preceding software development phase. The coding process should be a simple transition from the module specifications and, in particular, the pseudocode. Complete mspecs and properly developed pseudocode leaves little to interpretation for the coding phase, thus reducing the chance of error.

The importance of coding style (how it looks) is not as great as the rules that facilitate comprehension of the logical flow (how it relates). In the same light, in-line code documentation (comments) should most often address "why" rather than "how" functionality is implemented. These two focuses help the code reader understand the context in which a given segment of code is used. With precious few exceptions (e.g., high-performance device drivers), quality source code should be recognized by its readability and not by its raw size (number of lines) or its ability to take advantage of processor features.

8.14.1 Structured Coding Techniques

The goal of structured coding is to linearize control flow through a computer program so that the execution sequence follows the sequence in which the code is written. The dynamic structure of a program as it executes then resembles the state structure of the written text. This enhances readability of code, which eases understanding, debugging, testing, documentation, and modification of programs. It also facilitates formal verification of programs. Linear flow of control can be achieved by restricting the set of allowed program constructs to single-entry, single-exit formats. However, strict adherence to nested, single-entry, single-exit constructs leads to questions concerning efficiency; questions about reasonable violations of single entry, single exit; and questions about the proper role of the GOTO statement in structured coding.

8.14.2 Single-Entry, Single-Exit Constructs

In 1966, Bohm and Jacopini published a paper in which they demonstrated that sequencing, selection among alternative actions, and iteration are a sufficient set of constructs for describing the control flow of every conceivable algorithm. They argued that every Turing machine program can

be written in this manner. Because the Turing machine is the fundamental model of computation, it follows that every algorithm can be written using sequencing, selection, and iteration.

A modified version of the Bohm–Jacopini theorem can be stated as follows:

> Any single-entry, single-exit program segment that has all statements on some path from the entry to the exit can be using only sequencing, selection, and iteration.

A sufficient set of single-entry, single-exit constructs for specifying control flow in algorithms is as follows:

- Sequencing: S1; S2; S3
- Selection: IF B THEN S1 ELSE S2
- Iteration: WHILE B DO S

The single-entry, single-exit nature of these constructs is illustrated in Figure 8.1.

The single-entry, single-exit property permits nesting of constructs within one another in any desired fashion. Each statement Si might be an assignment statement, a procedure call, an IF... THEN... ELSE or a WHILE... DO. Statements of the latter forms may, in turn, contain nested statements. The most important aspect of the single-entry, single-exit property is that linearity of control flow is retained, even with arbitrarily deep nesting of constructs. The set of structured constructs selected for use in any particular application is primarily a matter of notational convenience. However, the selected constructs should be conceptually simple and widely applicable in practice (Table 8.5).

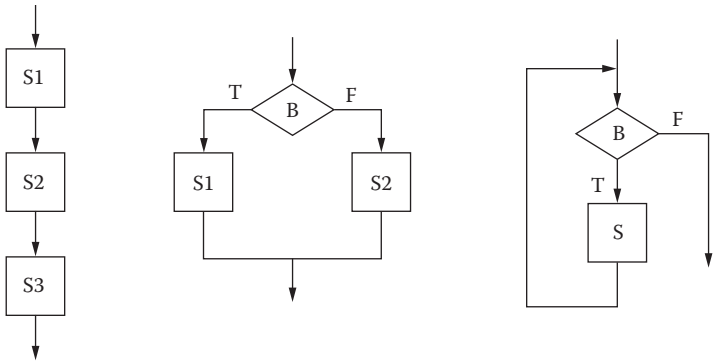

FIGURE 8.1 Single-entry, single-exit construct example.

TABLE 8.5
A Comparison of Code Inspections and Code Walk-Throughs

Properties	Inspections	Walk-Throughs
Formal moderator training	Yes	No
Distinct participant roles	Yes	No
Who "drives" the inspection or walk-through	Moderator	Author
Checklists for finding errors	Yes	No
Focused review effort—looks for the most frequently found kinds of errors	Yes	No
Formal follow-up to reduce bad fixes	Yes	No
Fewer future errors because of detailed error feedback to individual programmers	Yes	Incidental
Improved inspection efficiency from analysis of results	Yes	No
Analysis of data leading to detection of problems in the process, which in turn leads to improvements in the process	Yes	No

8.14.3 Good Coding Practices

Since coding is the primary output of software construction, a key question in managing construction is "How does one encourage good coding practices?" In general, mandating a strict set of standards from the top is not a good idea. Programmers tend to view managers as being at a lower level of technical evolution, and if there are going to be programming standards, programmers need to buy into them.

Standards should not be imposed at all, if they can be avoided. In contrast, flexible guidelines, a collection of suggestions rather than guidelines or a set of examples that embody the best practices, may be an alternative to standards. The following are several techniques for achieving good coding practices, techniques that are not as heavy-handed as laying down rigid coding standards.

8.14.3.1 Review Every Line of Code

A code review typically involves the programmer and at least two reviewers. That means that at least three people read every line of code. Another name for peer review is "peer pressure." In addition to providing a safety net in case the original programmer leaves the project, reviews improve code quality because the programmer knows that the code will be read by others. Even if your shop has not created explicit coding standards, reviews provide a subtle way of moving toward a group coding standard—decisions are made by the group during reviews, and over time, the group will derive its own standards.

8.14.3.2 Require Coding Sign-Offs

In other fields, technical drawings are approved and signed by the managing engineer. The signature means that to the best of the engineer's knowledge, the drawings are technically competent and error-free. Some companies treat software code the same way. Before code is considered to be complete, senior technical personnel must sign the code listing.

8.14.3.3 Route Good Code Examples for Review

A big part of good management is communicating objectives clearly. One way to communicate objectives is to circulate good code to programmers or post it for public display. In doing so, you provide a clear example of the quality you are aiming for. Similarly, a coding standards manual can consist mainly of a set of "best code listings." Identifying certain listings as "best" sets an example for others to follow. Such a manual is easier to update than an English-language standards manual and effortlessly presents subtleties in coding style that are hard to capture point by point in prose descriptions.

8.14.3.4 Emphasize That Code Listings Are Public Assets

Programmers sometimes feel that the code they have written is "their code," as if it were private property. Although it is the result of their work, code is part of the project and should be freely available to anyone else on the project who needs it. It should be seen by others during reviews and maintenance, even if at no other time.

8.14.3.5 Reward Good Code

Use your organization's reward system to reinforce good coding practices. Keep these considerations in mind as you develop your reinforcement system:

- The reward should be something the programmer wants. Many programmers find "atta-boy" rewards distasteful, especially when they come from nontechnical managers.
- Code that receives an award should be exceptionally good. If you give an award to a programmer everyone else knows does bad work, you look foolish. It does not matter that the programmer has a cooperative attitude or always comes to work on time. You lose credibility if your reward does not match the technical merits of the situation.

8.14.3.6 One Easy Standard

If you are managing a programming project and you have a programming background, an easy and effective technique for eliciting good work is to say "I must be able to read and understand any code written for the project." This may discourage clever or tricky code.

8.14.4 The Coding Process

Once the problem has been defined, the requirements listed, and the architecture and language selected, the program is ready to be implemented. Implementation (Figure 8.2) can be accomplished in a nearly standard order, although the steps may vary depending on the program to be written.

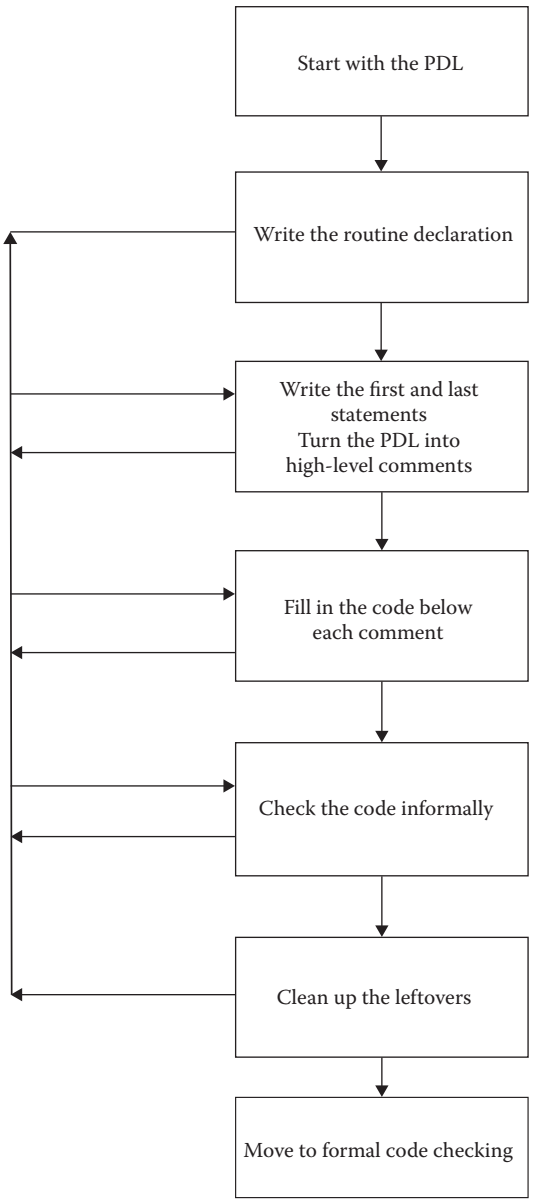

FIGURE 8.2 Coding implementation.

```
Keep track of current number of resources in use
  If another resource is available
     Allocate a dialog box structure
     If a dialog box structure could be allocated
     Note that one more resource is in use
          Initialize the resource
          Store the resource number at the location provided by the caller
     Endif
  Endif
  Return TRUE if a new resource was created; else return FALSE
```

FIGURE 8.3 Program Design Language example.

8.14.4.1 Start with a Program Design Language

Program Design Language (PDL) resembles English. However, it does not necessarily follow that any English-like description that collects one's thoughts will have roughly the same effect as any other. To use PDL effectively,

- Use English-like statements that precisely describe specific operations
- Avoid syntactic elements from the target programming language
- Write PDL at the level of intent
- Write PDL at a low enough level that generating code from it will be nearly automatic

Figure 8.3 is an example of PDL.

8.14.4.2 Writing the Routine Declaration

Write the routine interface statement. Turn the original header comment into a programming-language comment. Leave it in position above the PDL you have already written. This is a good time to make notes about any interface assumptions.

8.14.4.3 Turning the PDL into High-Level Comments

Write the first and last statements. Then turn the PDL into comments. At this point, the character of the routine is evident. The design work is complete and one can sense how the routine works even without seeing any code. Converting the PDL into programming-language code should feel mechanical, natural, and easy. If not, continue designing in PDL until the design feels solid.

8.14.4.4 Fill in the Code below Each Comment

Fill in the code below each line of the PDL comment. This requires an outline and then a paragraph for each point in the outline. Each PDL comment describes a block or paragraph of code. Like the lengths of literary paragraphs, the lengths of code paragraphs vary according to the thought being expressed. The quality of the paragraphs depends on the vividness and focus of the thoughts in them. This is the start on the code.

Each comment has given rise to one or more lines of code. Each block of code forms a complete thought based on the comment. The comments have been retained to provide a higher-level explanation of the code. All the variables that have been used have been declared at the top of the routine.

8.14.4.5 Check the Code Informally

Mentally test each block of code as it is filled in below its comment. Think of what it would take to break that block, and then prove that it will not happen. Once the routine is implemented, check it for mistakes. Sometimes, an important problem does not appear until the routine is implemented.

A problem might not appear until coding for several reasons. An error in the PDL might become more apparent in the detailed implementation logic. A design that looks elegant in PDL might

become clumsy in the implementation language. Working with the detailed implementation might disclose an error in the architecture or the requirements analysis. Additionally, the code might have a coding error. For all these reasons, the code should be checked before moving to the next step.

8.14.4.6 Clean Up the Leftovers

When the code has been checked for problems, it should be checked for general characteristics, including the following:

- Ensuring that all input and output data are accounted for.
- Ensuring that the routine does one thing and does it well, is loosely coupled to other routines, and is designed defensively.
- Checking for inaccurate variable names, unused data, and undeclared data.
- Checking for off-by-one errors, infinite loops, and improper nesting.
- Ensuring that white space has been used to clarify the logical structure of the routine, expressions, and parameter lists.
- Ensuring that the PDL that was translated into comments is still accurate. Check for algorithm descriptions, for documentation on interface assumptions and nonobvious dependencies, and for justification of unclear coding practices.

8.14.4.7 Check the Code Formally

After designing and implementing the routine, the next step is checking to be sure that what you have constructed is correct. Activity includes the following:

- Mentally checking the routine for errors
- Compiling the routine
- Using the computer to check the routine for errors
- Removal of errors from the routine

Remember, any errors that are missed at this stage will not be found until later testing. They are more expensive to find and correct then, so due diligence should be employed here.

8.14.5 Using Static Analysis to Check Code

Static analysis is the analysis of source code without execution. Static analysis can be done manually, like inspections, or can be automated by using software tools. Because static analysis does not require execution of the code, analysis for errors and vulnerabilities can be done throughout the software development process, and analysis can be conducted across all code paths. With dynamic analysis practices like testing, the line coverage is determined by the lines of code executed by the suite of test cases.

Static analysis is usually conducted by looking for error signatures or patterns that have caused problems in earlier programs. However, these signatures may be ambiguous, and static analysis suffers from a high number of false positives. Also, static analysis is limited by the current or known knowledge of error signatures and patterns. New vulnerabilities may not be detected by static analysis tools. There is ongoing research to investigate these problems and make static analysis a viable component of software development.

The sophistication of the analysis performed by tools varies from those that only consider the behavior of individual statements and declarations to those that include the complete source code of a program in their analysis. Uses of the information obtained from the analysis vary from highlighting possible coding errors to formal methods that mathematically prove properties about a given program (e.g., its behavior matches that of its specification).

Some of the implementation techniques of formal static analysis include the following:

- Model checking considers systems that have finite state or may be reduced to finite state by abstraction.
- Data flow analysis is a lattice-based technique for gathering information about the possible set of values.
- Abstract interpretation models the effect that every statement has on the state of an abstract machine (i.e., it "executes" the software based on the mathematical properties of each statement and declaration). This abstract machine overapproximates the behaviors of the system: the abstract system is thus made simpler to analyze, at the expense of *incompleteness* (not every property true of the original system is true of the abstract system). If properly done, though, abstract interpretation is *sound* (every property true of the abstract system can be mapped to a true property of the original system). The Frama-C framework and Polyspace heavily rely on abstract interpretation.
- Use of assertions in program code as first suggested by Hoare logic. There is tool support for some programming languages (e.g., the SPARK programming language [a subset of Ada] and the Java Modeling Language—JML—using ESC/Java and ESC/Java2, ANSI/ISO C Specification Language for the C language).

Static analysis has several benefits:

- Static analysis is able to examine more execution paths than conventional testing.
- Static analysis can be applied early in the development cycle, thus providing significant time and cost savings.

There are several programs that perform static analysis. These include the following:

- Coverity
- Code sonar
- Klocwork
- FindBugs
- Fortify
- Polyspace

When running a static analysis, the program lists potential defects. Examples of such defects include the following:

- Buffer overrun
- Buffer underrun
- Cast alters value
- Ignored return value
- Division by zero
- Missing return statement
- Null pointer dereference
- Redundant condition
- Shift amount exceeds bit width
- Type overrun
- Type underrun
- Uninitialized variable
- Unreachable code
- Unused value
- Useless assignment

It is up to the software designer to check each listed defect and determine if each is actually a defect or a false positive. The biggest problem with static analysis programs is the very high number of false positives produced during an analysis.

The Food and Drug Administration (FDA) is currently using three programs to conduct static analysis on programs reviewed during an inspection that lack static analysis. The FDA has been known to request a copy of the software, send it to Rockville to have a static analysis run, and then return to the manufacturer to discuss defects that have been found. Unfortunately, since the FDA is not fully aware of how the software operates, they may present false positives to the manufacturer as actual defects. It will be left to the manufacturer to analyze each potential defect and determine if it is a true defect or a false positive. The programs currently in use by the FDA are the following:

- Coverity
- Code Sonar
- Klocwork

8.14.6 Implementation Checklist

After implementing the design, review these points to assure that the implementation is robust and error resistant:

- Compare the implementation to the design. The design should be accurately implemented. Minor differences between the design and the implementation can cause problems.
- Ensure no unnecessary assumptions have been made in the code. Check for any arbitrary aspect of the implementation.
- Examine the expressions in the code for overflow or underflow. Variables should be checked as well.
- Check for nested operators or other risky language idioms. Rewrite risky expressions using comparable yet safer expressions.
- Ensure the code does not contain arcane language that the average programmer would not understand.
- Although each function may perform a single task, assure that the task is implemented using a single code path. Avoid achieving a task using different code to implement various special codes.
- Assure that all memory that is referenced is memory that can be accessed.
- Check to determine if the code restricts the references to pointers to inputs and outputs to only the memory required to hold those inputs and outputs.
- Adding assertions and other debugging code to the implementations can reduce the time required to find any bugs hiding in the code.

8.15 DESIGN SUPPORT TOOLS

Software development is very labor intensive and is, therefore, prone to human error. In recent years, commercial software development support packages have become increasingly more powerful, less expensive, and readily available to reduce the time spent doing things that computers do better than people. Although selection of the right tools can mean up-front dedication of some of the most talented resources in a development team, it can bring about a significant long-term increase in group productivity.

Good software development houses have taken advantage of computer-aided software engineering (CASE) tools, which reduce the time spent generating clear and thorough design documentation. There are many advantages of automated software design packages. Formal documentation can

be used as proof of product development procedure conformance for agency approvals. Clear and up-to-date design documents facilitate improved communications between engineers, lending to more effective and reliable designs. Standard documentation formats reduce learning curves associated with unique design depictions among software designers, leading to better and more timely design formulation. Total software life cycle costs are reduced, especially during maintenance, due to reduced ramp-up time and more efficient and reliable modifications. Finally, electronic forms of documentation can be easily backed up and stored off-site, eliminating a crisis in the event of an environmental disaster. In summary, the adaptation of CASE tools has an associated up-front cost, which is recovered by significant improvements in software quality and development time predictability.

8.16 DESIGN AS THE BASIS FOR VERIFICATION AND VALIDATION ACTIVITY

Verification is the process of assuring that all products of a given development phase satisfy given expectations. Prior to proceeding to the next/lower level or phase of design, the product (or outputs) of the current phase should be *verified* against the inputs of the previous stage. A design process cannot be a "good" process without the verification process ingrained. That is, they naturally go hand in hand.

Software project management plans (or software quality assurance plans) should specify all design reviews. Each level of design will generate documentation to be reviewed or deliverables to verify against the demands of the previous stage. For each type of review, the software management plans should describe the purpose, materials required, scheduling rules, scope of review, attendance expectations, review responsibilities, what the minutes should look like, follow-up activities, and any other requirements that relate to company expectations.

At the code level, code reviews should assure that the functionality implemented within a routine satisfies all expectations documented in the mspecs. Code should also be inspected to satisfy all coding rules.

The output of good software designs also includes *implementation requirements*. At minimum, implementation requirements include the rules and expectations placed on the designers to assure design uniformity as well as constraints, controls, and expectations placed on designs to ensure that upper-level requirements are met. General examples of implementation requirements might include rules for accessing I/O ports, timing requirements for memory accesses, semaphore arbitration, intertask communication schemes, memory addressing assignments, and sensor or device control rules. The software verification and validation process must address implementation requirements as well as the upper-level software requirements to that ensure the product works according to its specifications.

8.17 CONCLUSION

Software, in and as a medical device, is subjected to a rigorous, multistaged design process to assure that it is safe, effective, and reliable for its intended use. After taking the requirements from the Software Requirements Specification including reviewing current standards and regulations for appropriate requirements, the top level design consists of the following:

- Establishing the software architecture
- Choosing a methodology and a language
- Estimating the potential risks the software might produce
- Defining appropriate metrics to evaluate the design
- Checking for design completeness by use of an RTM
- Conducting various types of software reviews at appropriate times throughout the process

The detailed design consists of the following:

- Predicting real-time performance
- Conducting design simulation
- Repairing module specifications
- Coding the design
- Using support tools where appropriate

If done properly, the design will form the basis for the next phase in the development process, verification and validation. In addition to producing a safe and effective program, this process will also help reduce coding time. In the final analysis, the patient, the user, and the developer will all benefit from implementation of this structured development process.

EXERCISES

1. You are responsible for developing the software embedded in an oximeter. The software must run a self-test upon start-up. Determine saturated oxygen in the blood from a finger clip, determine the heart rate, and report the results on a screen. It must also interface with an anesthesia machine and display its data on the monitor. Establish a plan for developing the software.
2. What are some of the possible design alternatives and trade-offs for the device?
3. Develop the architecture for the software. What are the most important considerations when developing the architecture?
4. Explain the pros and cons of using object-oriented designs on this project versus structured analysis.
5. List some of the risk analysis activities for this project. Explain how doing a fault tree analysis early in the development process would help in establishing the program.
6. Check the IEEE website (http://standards.ieee.org/software/) for a list of standards documents that would assist in the development and testing of this software.
7. Explain how the design would assist in your verification and validation activities.

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9 Human Factors

> In the sick room, ten cents' worth of human understanding equals ten dollars' worth of medical science.
>
> **Martin H. Fischer**

Somewhere, it is likely that a person is driving in the wrong direction on a one-way road. Somewhere else, someone is driving without headlights, although he/she is needing them but cannot determine how to turn them on. A student just flunked an exam by using the wrong answer sheet. Several folks are trying to go in the out door... Poor labeling, distractions, and other factors may be to blame here. For the purposes of this text, we will concern ourselves with the need to account for this in device design via the use of human factors studies.

Human factors engineering, also called ergonomics, can trace its roots to early industrial engineering studies of work efficiency and task performance using, for example, time-motion techniques. Human factors engineering emerged as a recognized discipline during World War II while focusing primarily on military system performance, including problems in signal detection, workspace constraints, and optimal task training. The widespread recognition of the importance of applying human factors engineering in the design of tools, devices, tasks, and other human activities is reflected in the increasing number of disparate professionals interested in human factors. Their work products can be found in lay and professional publications, standards, and other documents. Human factors activities have improved the quality of personal and professional life across many domains. Public and professional interest in patient safety issues has promoted increased application of human factors engineering to the medical domain.

Numerous medical device companies have established human factors engineering programs to ensure the usability and safety of their devices. These companies also believe that their human factors engineering efforts enhance the marketability of their products. National and international regulations with respect to the safety of medical devices now require that human factors engineering principles be applied to the design of medical devices and that this process be documented.

9.1 WHAT IS HUMAN FACTORS?

Human factors is defined as the application of the scientific knowledge of human capabilities and limitations to the design of systems and equipment to produce products with the most efficient, safe, effective, and reliable operation. This definition includes several interesting concepts.

Although humans are capable of many highly technical, complex, or intricate activities, they also have limitations to these activities. Of particular interest to the medical designer are natural limitations due to physical size, range of motion, visual perception, auditory perception, and mental capabilities under stress. Although the user may be characterized by these limitations, the designer cannot allow them to adversely affect the safety, effectiveness, or reliability of the device. The designer should therefore identify and address all possible points of interface between the user and the equipment, characterize the operating environment, and analyze the skill level of the intended users.

Interface points are defined as those areas that the user must control or maintain in order to derive the desired output from the system. Interface points include control panels, displays, operating procedures, operating instructions, and user training requirements.

The environment in which the device will be used must also be characterized to determine those areas that may cause problems for the user, such as lighting, noise level, temperature, criticality of the operation, and the amount of stress the user is experiencing while operating the system. The design must then be adjusted to eliminate any potential problems.

The skill level of the user is an important parameter to be analyzed during the design process and includes such characteristics as educational background, technical expertise, and (normally) computer knowledge. To assure that the user's skill levels have been successfully addressed, the product should be designed to meet the capabilities of the least skilled *potential* user. Designing to meet this worst-case situation will assure that the needs of the majority of potential users will be satisfied.

The final and most important activity in human factors engineering is determining how these areas interact within the particular device. The points of interface are designed based on the anticipated operating environment and on the skill level of the user. The skill level may depend not only on the education and experience of the user but on the operating environment, as well. To design for such interaction, the designer must consider the three elements that comprise human factors: the human element, the hardware element, and the software element.

9.2 THE HUMAN ELEMENT IN HUMAN FACTORS ENGINEERING

The human element addresses several user characteristics, including memory and knowledge presentation, thinking and reasoning, visual perception, dialogue construction, individual skill level, and individual sophistication. Each is an important factor in the design consideration.

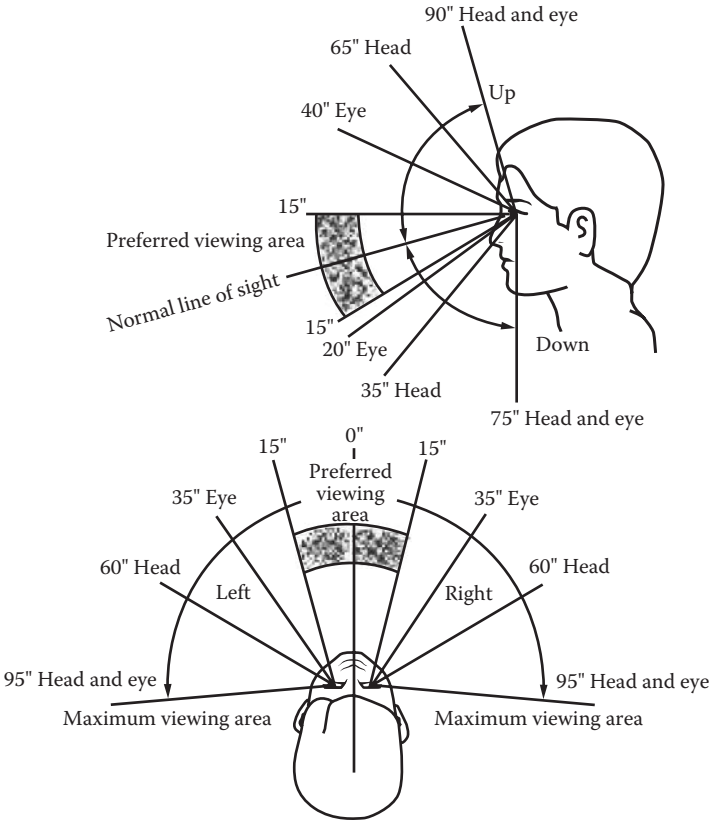
A human being has two types of memory. Short-term memory deals with sensory input, such as visual stimuli, sounds, and sensations of touch. Long-term memory is composed of our knowledge database. If the human–machine interface makes undue demands on either short- or long-term memory, the performance of the individual in the system will be degraded. The speed of this degradation depends on the amount of data presented, the number of commands the user must remember, and/or the stress involved in the activity.

When humans perform a problem-solving activity, they usually apply a set of guidelines or strategies based on their understanding of the situation and their experiences with similar types of problems, rather than applying formal inductive or deductive reasoning techniques. The human–machine interface must be specific in a manner enabling the user to relate to their previous experiences and develop guidelines for a particular situation.

The physical and cognitive constraints associated with visual perception must be understood when designing the human–machine interface. For example, studies have shown that since the normal line of sight is within 15° of the horizontal line of sight, the optimum position for the instrument face is within a minimum of 45° of the normal line of sight (Figure 9.1). Other physical and cognitive constraints have been categorized and are available in references located at the end of this chapter.

When people communicate with one another, they communicate best when the dialogue is simple, easy to understand, direct, and to the point. The designer must assure that device commands are easy to remember; error messages are simple, direct, and not cluttered with computer jargon; and help messages are easy to understand and pointed. The design of dialogue should be addressed to the least skilled potential user of the equipment.

Typical users of a medical device are not familiar with hardware design or computer programming. They are more concerned with the results obtained from using the device than about how the results were obtained. They want a system that is convenient, natural, flexible, and easy to use. They do not want a system that looks imposing, is riddled with computer jargon,



	Preferred	Maximum[a]		
		Eye rotation	Head rotation	Head and eye rotation
Up	15"	40"	65"	90"
Down	15"	20"	35"	75"
Right	15"	35"	60"	95"
Left	15"	35"	60"	95"

[a]Display area on the console defined by the angles measured from the normal line of sight.

FIGURE 9.1 Normal line of sight.

requires them to memorize many commands, or has unnecessary information cluttering the display areas.

In summary, the human element requires a device that has inputs, outputs, controls, displays, and documentation that reflect an understanding of the user's education, skill, needs, experience, and stress level when operating the equipment.

9.3 THE HARDWARE ELEMENT IN HUMAN FACTORS

The hardware element considers size limitations, the location of controls, compatibility with other equipment, the potential need for portability, and possible user training. It also addresses the height of the preferred control area and the preferred display area when the operator is standing (Figure 9.2)

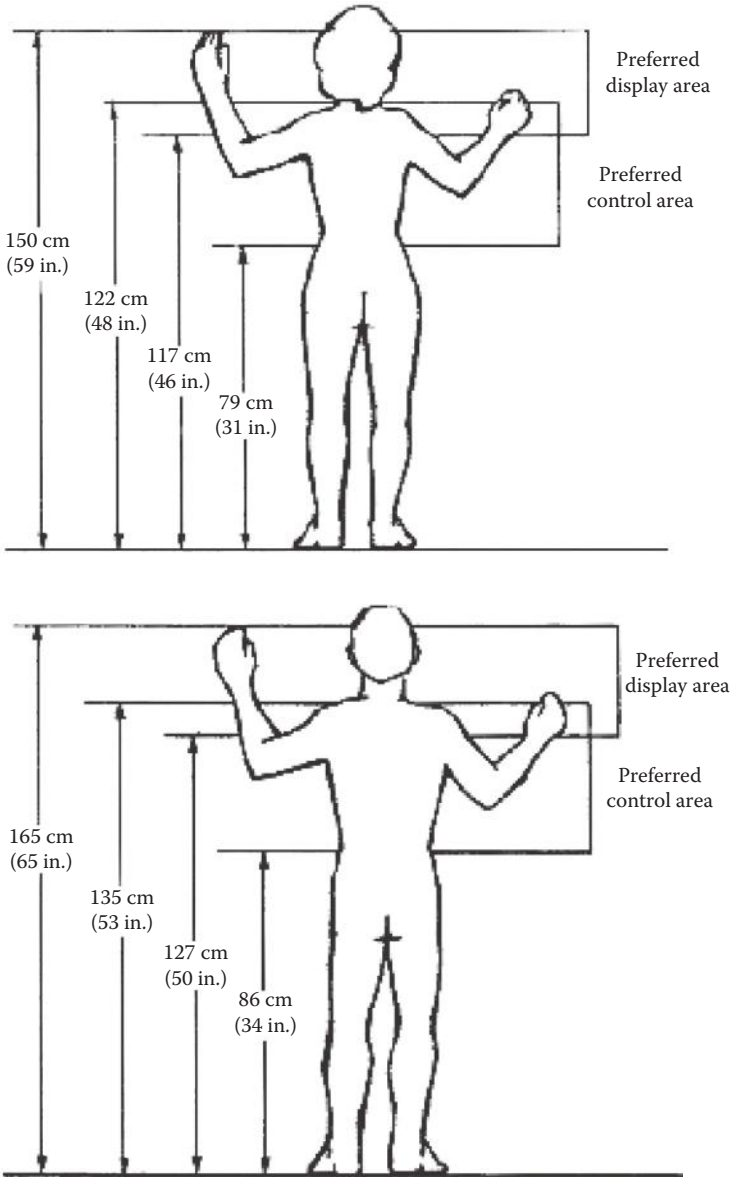


FIGURE 9.2 Display area when standing, typical female and male.

and when the operator is sitting (Figure 9.3), and the size of the human hand in relation to the size of control knobs or switches (Figure 9.4).

Hardware issues are best addressed by first surveying potential customers of the device to help determine the intended use of the device, the environment in which the device will be used, and the optimum location of controls and displays. Once the survey is completed and the results analyzed, a computer-based or a cardboard, foam, or wooden model of the device is built and reviewed with the potential customers. The customer can then get personal, hands-on experience with the controls, displays, and device framework and offer constructive criticism on the design. Once all changes have been made, the model can be transposed into a prototype, using actual hardware.

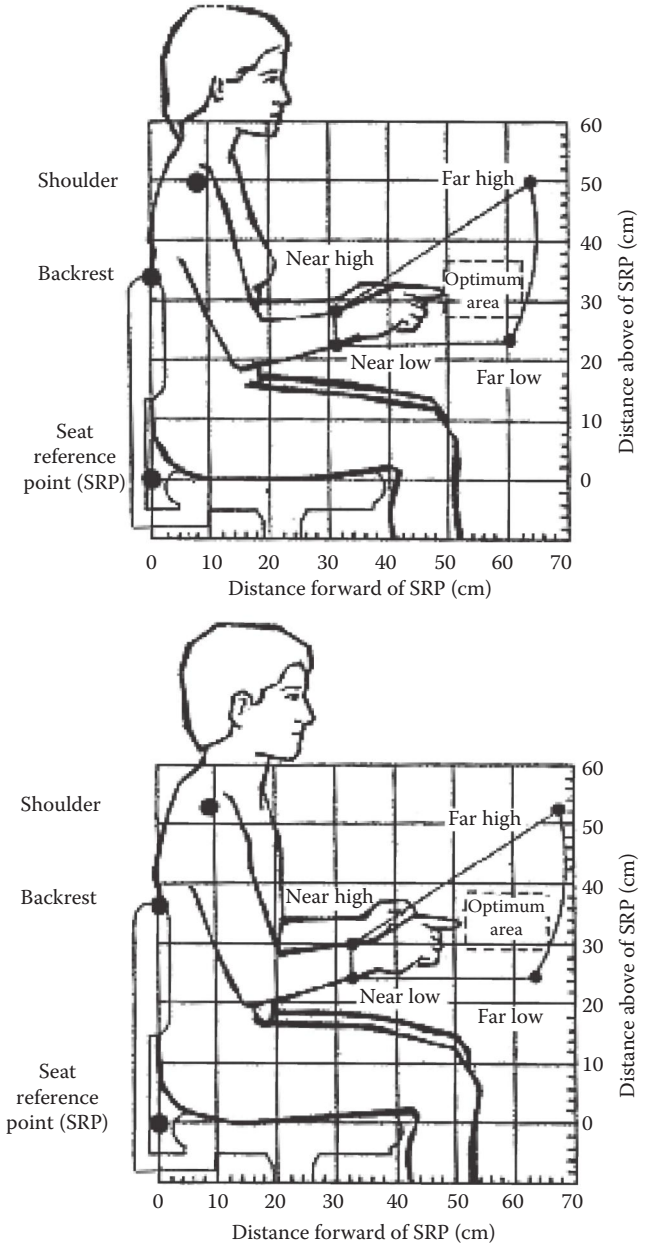
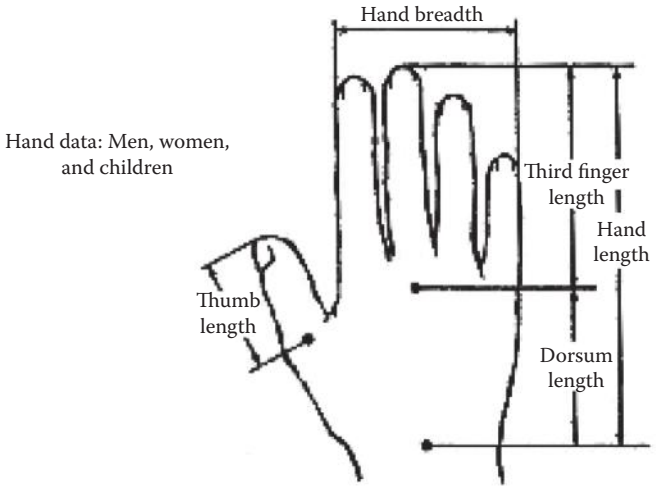


FIGURE 9.3 Display area when sitting.

9.4 THE SOFTWARE ELEMENT IN HUMAN FACTORS

The software element of the device must be easy to use and understand. It must have simple, reliable data entry; it should be menu driven if there are many commands to be learned; displays must not be overcrowded; and dialogue must not be burdened with computer jargon. The software must provide feedback to the user through error messages and help messages. An indication that the process is involved in some activity is also important, as a blank screen leads to the assumption that nothing is active, and the frustrated user starts pushing keys or buttons.



Hand data	Men			Women			Children			
	2.5% tile	50% tile	97.5% tile	2.5% tile	50% tile	97.5% tile	6 year	8 year	11 year	14 year
Hand length	173 mm (6.8 in.)	191 mm (7.5 in.)	208 mm (8.2 in.)	157 mm (6.2 in.)	175 mm (6.9 in.)	191 mm (7.5 in.)	130 mm (5.1 in.)	142 mm (5.2 in.)	160 mm (6.3 in.)	178 mm (7.0 in.)
Hand breadth	81 mm (3.2 in.)	89 mm (3.5 in.)	97 mm (3.8 in.)	66 mm (2.6 in.)	74 mm (2.9 in.)	79 mm (3.1 in.)	58 mm (2.3 in.)	64 mm (2.5 in.)	71 mm (2.8 in.)	–
Third finger length	102 mm (4.0 in.)	114 mm (4.5 in.)	127 mm (5.0 in.)	91 mm (3.6 in.)	100 mm (4.0 in.)	112 mm (4.4 in.)	74 mm (2.9 in.)	81 mm (3.2 in.)	89 mm (3.5 in.)	102 mm (4.0 in.)
Dorsum length	71 mm (2.8 in.)	75 mm (3.0 in.)	81 mm (3.2 in.)	66 mm (2.6 in.)	74 mm (2.9 in.)	79 mm (3.1 in.)	56 mm (2.2 in.)	61 mm (2.4 in.)	71 mm (2.8 in.)	75 mm (3.0 in.)
Thumb length	61 mm (2.4 in.)	69 mm (2.7 in.)	75 mm (3.0 in.)	56 mm (2.2 in.)	61 mm (2.4 in.)	66 mm (2.6 in.)	46 mm (1.8 in.)	51 mm (2.0 in.)	56 mm (2.2 in.)	61 mm (2.4 in.)

Additional data: Average man

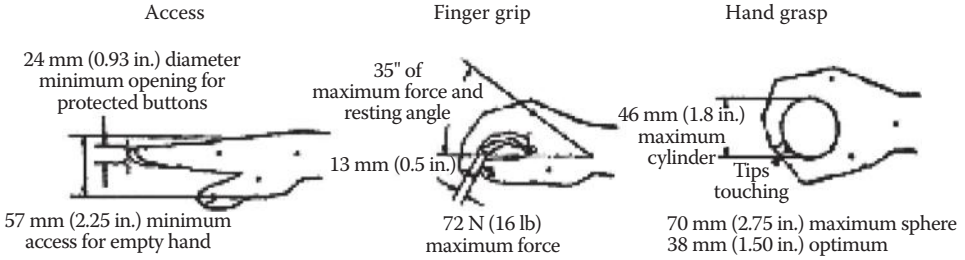


FIGURE 9.4 Hand sizes.

Software must be designed considering the environment in which it is to be used, especially with regard to colors of displays, type of data to be displayed, format of the data, alarm levels to be used, and so forth. Stress and fatigue can be reduced by consideration of color and the intensity of the displayed data. Operator effectiveness can be improved by optimizing the location of function keys, displaying more important data in the primary viewing area, and placing secondary data in the secondary display area. The inclusion of device checkout procedures and menus also improves operator effectiveness and confidence.

9.5 THE HUMAN FACTORS PROCESS

Human factors is the sum of several processes including the analytic process that focuses on the objectives of the proposed device and the functions that should be performed to meet those

objectives; the design and development process that converts the results of the analyses into detailed equipment design features; and the test and evaluation process that verifies that the design and development process has resolved issues identified in the analytic process.

Human factors engineering integrations begin with early planning and may continue throughout the life cycle of the device. As a minimum, human factors should continue until the device is introduced commercially. Human factors efforts following commercial introduction are important to the enhancement of the device and the development of future devices.

9.6 PLANNING

A human factors plan should be developed as an integral part of the overall plan for device development. The plan should guide human factors efforts in the interrelated processes of analysis, design and development, and test and evaluation. The plan should describe human factors tasks necessary to complete each process, the expected results of those tasks, the means of coordinating those tasks with the overall process for device development, and the schedule for that coordination. The plan should address the resources necessary for its accomplishment including levels of effort necessary for its management and coordination as well as for accomplishment of its individual tasks.

The plan should assure that results of human factors tasks are available in time to influence the design of the proposed device as well as the conduct of the overall project. Analysis tasks should begin very early. Iterations of analysis tasks that refine earlier products may continue throughout the project. Design and development build on the products of early analysis, and iterations may also continue throughout the project. Test and evaluation should begin with the earliest products of design and development. The results of test and evaluation should influence subsequent iterations of analysis, design and development, and test and evaluation tasks.

9.7 ANALYSIS

Successful human factors is predicated on careful analyses. Early analyses should focus on the objectives of the proposed device and the functions that should be performed to meet those objectives. Later analysis should focus on the critical human performance required of specific personnel as a means of establishing the human factors parameters for design of the device and associated job aids, procedures, and training and for establishing human factors test and evaluation criteria for the device. Analyses should be updated as required to remain current with the design effort.

9.8 CONDUCT USER STUDIES

The goal of user studies is to learn as much as possible within a reasonable time frame about the customer's needs and preferences as they relate to the product under development. Several methods are available for getting to know the customer.

9.8.1 Observations

Observations are a productive first step toward getting to know the user. By observing people at work, a rapid sense for the nature of their jobs is developed, including the pace and nature of their interactions with the environment, coworkers, patients, equipment, and documents. Such observations may be conducted in an informal manner, possibly taking notes and photographs. Alternatively, a more formal approach may be taken that includes rigorous data collection, including videotaping. For example, it may be important to document a clinician's physical movements and the time they spend performing certain tasks to determine performance benchmarks. This latter approach is referred to as a time-motion analysis and may be warranted if one of the design goals is

to make the customer more productive. An analysis of the process using a process chart (see 2.3.1) may be warranted.

Enough time should be spent observing users to get a complete sense for how they perform tasks related to the product under development. A rule of thumb in usability testing is that 5–8 participants provide 80%–90% of the information you seek. The same rule of thumb may be applied to observations, presuming that you are addressing a relatively homogenous user population. Significant differences in the user population (i.e., a heterogeneous user population) may warrant more extensive observations. For example, it may become necessary to observe people who have different occupational backgrounds and work in different countries.

Designers and engineers should conduct their own observations using themselves as subjects. For starters, such observations increase empathy for the customer. Also, first-hand experience is always more powerful than reading a marketing report.

9.8.2 Interviews

Similar to observations, interviews provide a wealth of information with a limited investment of time. Structured interviews based on scripted questions are generally better than unstructured interviews (i.e., a free-flowing conversation). This is because a structured interview assures that the interviewer will ask everyone the same question, enabling a comparison of answers. Structured interviews may include a few open-ended questions to produce and evoke comments and suggestions that could not be anticipated. The interview script should be developed from a list of information needs. Generally, questions should progress from general to more specific design issues. Care should be taken to avoid mixing marketing- and engineering-related concerns with usability concerns.

Interviews can be conducted just after observations are completed. Conducting the interviews prior to the observations can be problematic as it tends to alter the way people react.

9.8.3 Focus Groups

Conducting interviews with people in their working environment (sometimes referred to as contextual interviewing) is generally best. Interviewees are likely to be more relaxed and opinionated. Interviews conducted at trade shows and medical conferences, for example, are more susceptible to bias and may be less reliable. However, this exposure may allow for the ability to obtain a large number of data points quickly and thus should not be discounted as an approach. Additionally, this allows for premarketing of your product and potential requests for sites to assist in preclinical testing.

Conducting interviews with a group of 5–10 people at a time enables easy determination of a consensus on various design issues. In preparation for such a focus group, a script should be developed from a set of information requirements. Use the script as a guide for the group interview, but feel free to let the discussion take a few tangents if they are productive ones. Also, feel at liberty to include group exercises, such as watching a video or ranking and rating existing products, as appropriate.

Conduct enough focus groups to gain confidence that an accurate consensus has been developed. Two focus groups held locally may be enough if regional differences of opinion are unlikely and the user group is relatively homogenous. Otherwise, it may be appropriate to conduct up to four groups each at domestic and international sites that provides a reasonable cross-section of the marketplace.

Document the results in a focus groups report. The report can be an expanded version of the script. Begin the report with a summary section to pull together the results. Findings (i.e., answers to questions) may be presented after each question. The findings from various sites may be integrated or presented separately, depending on the design issue and opportunity to tailor the product under

development to individual markets. Results of group exercises may be presented as attachments and discussed in the summary.

9.8.4 Task Analysis

The purpose of task analysis is to develop a detailed view of customer interactions with a product by dividing the interactions into discrete actions and decisions. Typically, a flowchart is drawn that shows the sequence and logic of customer actions and decisions. The task analysis is extended to include tables that define information and control requirements associated with each action and decision. In the course of the task analysis, characterize the frequency, urgency, and criticality of integrated tasks, such as "checking the breathing circuit."

9.8.5 Benchmark Usability Test

The start of a new product development effort is a good time to take stock of the company's existing products. An effective way to do this is to conduct a benchmark usability test that yields, in a quantitative fashion, both objective and subjective measures of usability. Such testing will identify the strengths and weaknesses of the existing products, as well as help establish usability goals for the new product.

9.8.6 Write User Profile

To culminate the user study effort, write a so-called user profile. A user specification (two to five pages) summarizes the important things learned about the customers. The profile should define the user population's demographics (age, gender, education level, occupational background, language); product-related experience; work environment; and motivation level. The user profile is a major input to the user specification that describes the product under development from the customer's point of view.

9.8.7 Set Up an Advisory Panel

To assure early and continued customer involvement, set up an advisory panel that equitably represents the user population. The panel may include three to five clinicians for limited product development efforts or be twice as large for larger efforts. The panel participants are usually compensated for their time. Correspond with members of the panel on an as-needed basis and meet with them periodically to review the design in progress. Note that advisory panel reviews are not an effective replacement for usability testing.

9.9 SET USABILITY GOALS

Usability goals are comparable to other types of engineering goals in the sense that they are quantitative and provide a basis for acceptance testing. Goals may be objective or subjective. A sample objective goal might be as follows: on average, users shall require 3 seconds to silence an alarm. This goal is an objective goal because the user's performance level can be determined simply by observation. For example, you can use a stopwatch to determine task times. Other kinds of objective goals concentrate on the number of user errors and the rate of successful task completion.

A sample subjective goal is as follows: on average, 75% of users shall rate the intuitiveness of the alarm system as 5 or better, where 1 = poor and 7 = excellent. The scale and responses are designed to be integer in nature to allow ease of data entry ("Likert"). This goal is subjective because it requires asking the users' opinions about their interaction with the given product. A rating sheet can

be used to record their answers. Other kinds of subjective goals concentrate on mental processing and emotional response attributes, such as learning, frustration level, fear of making mistakes, and so forth.

Every usability goal is based on a usability attribute, for example, task, speed, or intuitiveness; includes a metric such as time or scale; and sets a target performance level, such as 3 seconds or a rating of 5 or better.

Typically, up to 50 usability goals may be written, two-thirds of which are objective and one-third of which are subjective. The target performance level on each goal is based on findings from preceding user studies, particularly the benchmark usability testing. If there is no basis for comparison, that is, there are no comparable products, then engineering judgment must be used to set the initial goals and adjust them as necessary to assure they are realistic.

9.10 DESIGN USER INTERFACE CONCEPTS

Concurrent design is a productive method of developing a final user interface design. It enables the thorough exploration of several design concepts before converging on a final solution. In the course of exploring alternative designs, limited prototypes should be built of the most promising concepts and user feedback obtained on them. This gets users involved in the design process at its early stages and assures that the final design will be closely matched to users' expectations.

Note that the design process steps described here assume that the product includes both hardware and software elements. Some steps would be moot if the product has no software user interface.

9.10.1 Develop Conceptual Model

When users interact with a product, they develop a mental model of how it works. This mental model may be complete and accurate or just the opposite. Enabling the user to develop a complete and accurate mental model of how a product works is a challenge. The first step involves developing so-called conceptual models of how to represent the product's functions. This exercise provides a terrific opportunity for design innovation. The conceptual model may be expressed as a bubble diagram, for example, that illustrates the major functions of the product and functional interrelationships as you would like the users to think of them. You can augment the bubble diagram with a narrative description of the conceptual model. (Alternatively, you can develop a concept map of your device's actions and attempt to manipulate this for better design inputs.)

9.10.2 Develop User Interface Structure

Develop alternative user interface structures that complement the most promising two to three conceptual models. These structures can be expressed in the form of screen hierarchy maps that illustrate where product functions reside and how many steps it will take users to get to them. Such maps may take the form of a single element, a linear sequence, a tree structure (cyclic or acyclic), or a network. In addition to software screens, such maps should show which functions are allocated to dedicated hardware controls.

9.10.3 Define Interaction Style

In conjunction with the development of the user interface structures, alternative interaction styles should be defined. Possible styles include question-and-answer dialogues, command lines, menus, and direct manipulation.

9.10.4 Develop Screen Templates

Determine an appropriate-sized display based on the user interface structure and interaction style, as well as other engineering considerations. Using computer-based drawing tools, draw the outline of a blank screen. Next, develop a limited number (perhaps three to five) of basic layouts for the information that will appear on the various screens. Normally, it is best to align all elements, such as titles, windows, prompts, and numerics, according to a grid system. (Many software packages exist for this purpose.)

9.10.5 Develop Hardware Layout

Apply established design principles in the development of hardware layouts that are compatible with the evolving software user interface solutions. Assure that the layouts reinforce the overall conceptual model. This will, in addition, be valuable for future documentation efforts.

9.10.6 Develop a Screenplay

Apply established design principles in the development of a detailed screenplay. Do not bother to develop every possible screen at this time. Rather, develop only those screens that would enable users to perform frequently used, critical, and particularly complex functions. Base the screen designs on the templates. Create new templates or eliminate existing templates as required while continuing to limit the total number of templates. Assure that the individual screens reinforce the overall conceptual model. You may choose to get user feedback on the screenplay (what some people call a paper prototype).

9.10.7 Develop a Refined Design and Final Design

The latter two steps describe prototyping and testing the user interface. These efforts will help determine the most promising design concept or suggest a hybrid of two or more concepts. The next step is to refine the preferred design. Several reiterations of the preceding steps may be necessary, including developing a refined conceptual model, developing a refined user interface structure, and developing an updated set of screen templates. Then, a refined screenplay and hardware layout may be developed, followed by a final design.

9.11 MODEL THE USER INTERFACE

Build a prototype to evaluate the dynamics of the user interface. Early prototypes of competing concepts may be somewhat limited in terms of their visual realism and how many functions they perform. Normally, it is best to develop a prototype that (1) presents a fully functional top level that allows users to browse their basic options and (2) enables users to perform a few sample tasks, that is, walk through a few scenarios. As much as possible, include tasks that relate to the established usability goals.

User interface prototypes may be developed using conventional programming languages or rapid prototyping languages, such as SuperCard or Altia Design and the like. The rapid prototyping languages are generally preferable because they allow for faster prototyping and they are easier to modify based on core project team and user feedback. Simpler drawing tools such as Visual Basic now are not generally worth the effort to use.

Early in the screenplay development process, it may make sense to prototype a small part of the user interface to assess design alternatives or to conduct limited studies, such as how frequently to flash a warning. Once detailed screenplays of competing concepts are available, build higher-fidelity prototypes that facilitate usability testing. Once a refined design is developed, build a fully

functional prototype that permits a verification usability test. Such prototypes can be refined based on final test results and serve as a specification.

9.12 TEST THE USER INTERFACE

There are several appropriate times to conduct a usability test, including the following:

- At the start of a development effort to develop benchmarks
- When you have paper-based or computer-based prototypes of competing design concepts
- When you have a prototype of your refined design
- When you want to develop marketing claims regarding the performance of the actual product

While the rigor of the usability test may change, based on the timing of the test, the basic approach remains the same. You recruit prospective users to spend a concentrated period of time interacting with the prototype product. The users may undertake a self-exploration or perform directed tasks. During the course of such interactions, you note the test participants' comments and document their performance. At intermittent stages, you may choose to have the test participants complete a questionnaire or rating/ranking exercise. Videotaping test proceedings is one way to give those unable to attend the test a first-hand sense of user–product interactions. Sometimes, it is useful to create a 10- to 15-minute highlight tape that shows the most interesting moments of all test sessions.

During testing, collect the data necessary to determine if you are meeting the established usability goals. This effort will add continuity and objectivity to the usability engineering process.

9.13 SPECIFY THE USER INTERFACE

9.13.1 Style Guide

The purpose of a style guide is to document the rules of the user interface design. By establishing such rules, you can check the evolving design to determine any inconsistencies. Also, it assures the consistency of future design changes. Style guides, usually 10–15 pages in length, normally include a description of the conceptual model, the design elements, and elements of style.

9.13.2 Screen Hierarchy Map

The purpose of a screen hierarchy map is to provide an overview of the user interface structure. It places all screens that appear in the screenplay in context. It enables the flow of activity to be studied in order to determine if it reinforces the conceptual model. It also helps to determine how many steps users will need to take to accomplish a given task. Graphical elements of the screen hierarchy map should be cross-indexed to the screenplay.

9.13.3 Screenplay

The purpose of a screenplay is to document the appearance of all major screens on paper. Typically, screen images are taken directly from the computer-based prototype. Ideally, the screenplay should present screen images in their actual scale and resolution. Each screen should be cross-indexed to the screen hierarchy map.

9.13.4 Specification Prototype

The purpose of the specification prototype is to model accurately the majority of user interface interactions. This provides the core project team with a common basis for understanding how the final product should work. It provides a basis for writing the user documentation. It may also be used to orient those involved in marketing, sales, and training.

9.13.5 Hardware Layouts

The hardware layout may be illustrated by the specification prototype. However, the hardware may not be located proximal to the software user interface. If this is the case, develop layout drawings to document the final hardware layout.

9.14 ADDITIONAL HUMAN FACTORS DESIGN CONSIDERATIONS

The design of medical devices should reflect human factors engineering design features that increase the potential for successful performance of tasks and for satisfaction of design objectives.

9.14.1 Consistency and Simplicity

Where common functions are involved, consistency is encouraged in controls, displays, markings, coding, and arrangement schemes for consoles and instrument panels.

Simplicity in all designs is encouraged. Equipment should be designed to be operated, maintained, and repaired in its operational environment by personnel with appropriate but minimal training. Unnecessary or cumbersome operations should be avoided when simpler, more efficient alternatives are available.

9.14.2 Safety

Medical device design should reflect system and personnel safety factors, including the elimination or minimization of the potential for human error during operation and maintenance under both routine and nonroutine or emergency conditions. Machines should be designed to minimize consequence of human error. For example, where appropriate, a design should incorporate redundant, diverse elements arranged in a manner that increases overall reliability when failure can result in the inability to perform a critical function.

Any medical device failure should immediately be indicated to the operator and should not adversely affect safe operation of the device. Where failures can affect safe operation, simple means and procedures for averting adverse effects should be provided.

When the device failure is life-threatening or could mask a life-threatening condition, an audible alarm and a visual display should be provided to indicate the device failure. Wherever possible, explicit notification of the source of failure should be provided to the user. Concise instructions on how to return to operation or how to invoke alternate backup methods should be provided.

9.14.3 Environmental/Organizational Considerations

The design of medical devices should consider the following:

- The levels of noise, vibration, humidity, and heat that will be generated by the device and the levels of noise, vibration, humidity, and heat to which the device and its operators and maintainers will be exposed in the anticipated operational environment

- The need for protecting operators and patients from electric shock, thermal, infectious, toxicological, radiologic, electromagnetic, visual, and explosion risks, as well as from potential design hazards, such as sharp edges and corners, and the danger of the device falling on the patient or operator
- The adequacy of the physical, visual, auditory, and other communication links among personnel and between personnel and equipment
- The importance of minimizing psychophysiological stress and fatigue in the clinical environment in which the medical device will be used
- The impact on operator effectiveness of the arrangement of controls, displays, and markings on consoles and panels
- The potential effects of natural or artificial illumination used in the operation, control, and maintenance of the device
- The need for rapid, safe, simple, and economical maintenance and repair
- The possible positions of the device in relation to the users as a function of the user's location and mobility
- The electromagnetic environment(s) in which the device is intended to be used

9.14.4 Documentation

Documentation is a general term that includes operator manuals, instruction sheets, online help systems, and maintenance manuals. These materials may be accessed by many types of users. Therefore, the documentation should be written to meet the needs of all target populations.

Preparation of instructional documentation should begin as soon as possible during the specification phase. This assists device designers in identifying critical human factors engineering needs and in producing a consistent human interface. The device and its documentation should be developed together.

During the planning phase, a study should be made of the capabilities and information needs of the documentation users, including the following:

- The user's mental abilities
- The user's physical abilities
- The user's previous experience with similar devices
- The user's general understanding of the general principles of operation and potential hazards associated with the technology
- The special needs or restrictions of the environment

As a minimum, the operator's manual should include detailed procedures for setup, normal operation, emergency operation, cleaning, and operator troubleshooting.

The operator manual should be tested on models of the device. It is important that these test populations be truly representative of end users and that they not have advance knowledge of the device.

Maintenance documentation should be tested on devices that resemble production units.

Documentation content should be presented in language free of vague and ambiguous terms. The simplest words and phrases that will convey the intended meaning should be used. Terminology within the publication should be consistent. Use of abbreviations should be kept to a minimum but defined where they are used.

Information included in warnings and cautions should be chosen carefully and with consideration of the skills and training of intended users. It is especially important to inform users about unusual hazards and hazards specific to the device.

Human factors engineering design features should assure that the device functions consistently, simply, and safely and that the environment, system organization, and documentation are analyzed

and considered in the design, thus increasing the potential for successful performance of tasks and for satisfaction of design objectives.

9.14.5 Anthropometry

Anthropometry is the science of measuring the human body and its parts and functional capacities. Generally, design limits are based on a range of values from the 5th-percentile female to the 95th-percentile male for critical body dimensions. The 5th-percentile value indicates that 5% of the population will be equal to or smaller than that value and 95% will be larger. The 95th-percentile value indicates that 95% of the population will be equal to or smaller than that value and 5% will be larger. The use of a design range from the 5th- to the 95th-percentile values will theoretically provide coverage from 90% of the user population for that dimension.

9.14.6 Functional Dimensions

The reach capabilities of the user population play an important role in the design of the controls and displays of the medical device. The designer should take into consideration both one- and two-handed reaches in the seated and standing positions (Figures 9.5 and 9.6).

Body mobility ranges should be factored into the design process. Limits of body movement should be considered relative to the age diversity and gender of the target user population.

The strength capacities of the device operators may have an impact on the design of the system controls. The lifting and carrying abilities of the personnel responsible for moving and/or adjusting the device need to be considered to assure that the device can be transported and adjusted efficiently and safely.

9.14.7 Psychological Elements

It is crucial to consider human proficiency in perception, cognition, learning, memory, and judgment when designing medical devices to assure that operation of the system is as intuitive, effective, and safe as possible.

9.14.8 Workstation Design Considerations

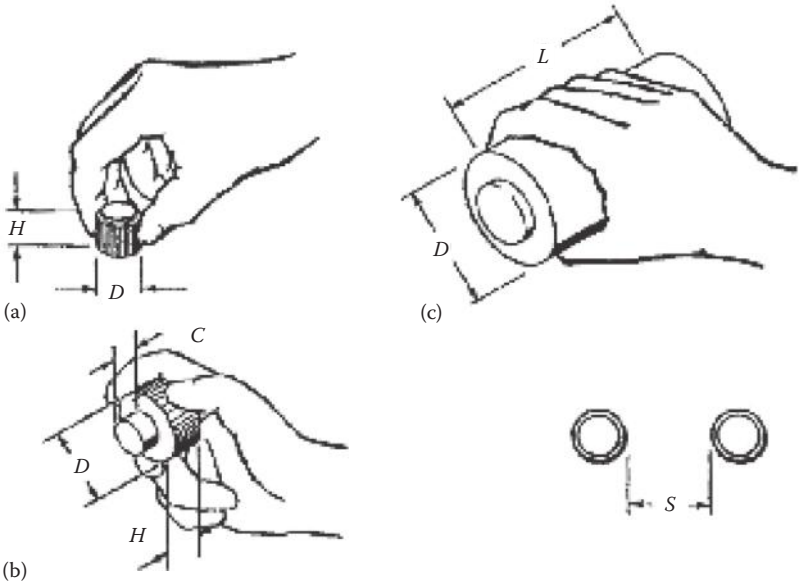
Successful workstation design is dependent on considering the nature of the tasks to be completed, the preferred posture of the operator, and the dynamics of the surrounding environment. The design of the workstation needs to take into account the adjustability of the furniture, clearances under work surfaces, keyboard and display support surfaces, seating, footrests, and accessories.

The effectiveness with which operators perform their tasks at consoles or instrument panels depends in part on how well the equipment is designed to minimize parallax in viewing displays, allow ready manipulation of controls, and provide adequate space and support for the operator.

A horizontal or nearly horizontal work surface serves primarily as a work or writing surface or as a support for the operator's convenience items. Certain types of controls, such as joysticks or tracking controls, can also be part of the surface design.

Controls should have characteristics appropriate for their intended functions, environments, and user orientations, and their movements should be consistent with the movements of any related displays or equipment components. The shape of the control should be dictated by its specific functional requirements. In a bank of controls, those controls affecting critical or life-supporting functions should have a special shape and, if possible, a standard location.

Controls should be designed and located to avoid accidental activation. Particular attention should be given to critical controls whose accidental activation might injure patients or personnel or



	Dimensions						
	(a) Finger grasp		(b) Thumb and fingers encircled			(c) Palm/hand grasp	
	Height, *H*	Diameter, *D*	Height, *H*	Diameter, *D*	Clearance, *C*	Diamter, *D*	Length, *L*
Minimum	13 mm (0.5 in.)	10 mm (0.375 in.)	13 mm (0.50 in.)	25 mm (1.0 in.)	16 mm (0.625 in.)	38 mm (1.5 in.)	75 mm (3.0 in.)
Maximum	25 mm (1.0 in.)	100 mm (4 in.)	25 mm (1.0 in.)	75 mm (3.0 in.)	—	75 mm (3 in.)	—

	Torque		Separation, *S*
	A	B	One hand individually
Minimum	—	—	25 mm (1.0 in.)
Preferred	—	—	50 mm (2.0 in.)
Maximum	32 mN m (4.5 in. oz.)	42 mN m (6.0 in. oz.)	—

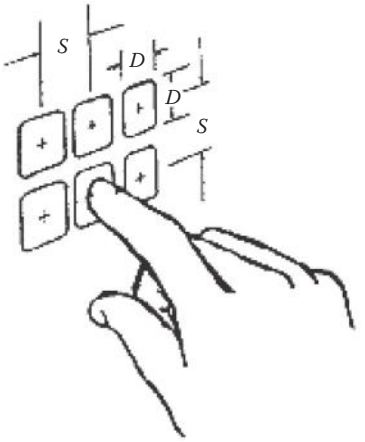
Notes: A, to and including 25 mm (1.0 in.) diameter knobs; B, greater than 25 mm (1.0 in.) diameter knobs.

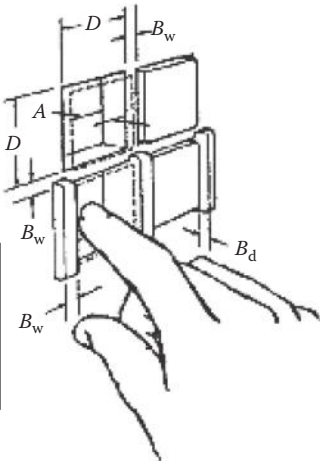
FIGURE 9.5 Example of functional dimensions (for knob input).

might compromise device performance. Feedback on control response adequacy should be provided as rapidly as possible.

9.14.9 Alarms and Signals

The purpose of an alarm is to draw attention to the device when the operator's attention may be focused elsewhere. Alarms should not be startling but should elicit the desired action from the user. When appropriate, the alarm message should provide instructions for the corrective action that is required. In general, alarm design will be different for a device that is continuously attended by a trained operator, such as an anesthesia machine, than for a device that is unattended and operated by





Touch switches

	Dimension, *D*	Spacing, *S*
Minimum	13 mm (0.50 in.)	19 mm (0.75 in.)
Maximum	38 mm (1.5 in.)	—

Pushbutton switches

	Dimension, *D*	Displacement, *A*	Separation/barriers[a]		Resistance
			B_w	B_d	
Minimum	19 mm (0.75 in.)	3 mm[b] (0.125 in.)	3 mm (0.125 in.)	5 mm (0.187 in.)	280 mN (10 oz)
Maximum	38 mm (1.5 in.)	6 mm (0.250 in.)	6 mm (0.250 in.)	6 mm (0.250 in.)	16.6 N (60 oz)

[a]Barriers shall have rounded edges.
[b]5 mm (0.188 in.) for positive position switches.

FIGURE 9.6 Example of functional dimensions (for button pressing).

an untrained operator, such as a patient-controlled analgesia device. False alarms, loud and startling alarms, or alarms that recur unnecessarily can be a source of distraction for both an attendant and the patient and thus be a hindrance to good patient care.

Alarm characteristics are grouped in the following three categories:

- High priority: a combination of audible and visual signals indicating that immediate operator response is required
- Medium priority: a combination of audible and visual signals indicating that prompt operator response is required
- Low priority: a visual signal, or a combination of audible and visual signals, indicating that operator awareness is required

A red flashing light should be used for a high-priority alarm condition unless an alternative visible signal that indicates the alarm condition and its priority is employed. A red flashing light should not be used for any other purpose.

A yellow flashing light should be used for a medium-priority alarm condition unless an alternative visible signal that indicates the alarm condition and it priority is employed. A yellow flashing light should not be used for any other purpose.

A steady yellow light should be used for a low-priority alarm condition unless an alternative visible signal that indicates the alarm condition and its priority is employed.

Audible signals should be used to alert the operator to the status of the patient or the device when the device is out of the operator's line of sight. Audible signals used in conjunction with visual displays should be supplementary to the visual signals and should be used to alert and direct the user's attention to the appropriate visual display. Some alarm information may be mandated by Food and Drug Administration (FDA) regulations; this information needs also to be checked.

Design of equipment should take into account the background noise and other audible signals and alarms that will likely be present during the intended use of the device. The lowest volume control settings of the critical life support audible alarms should provide sufficient signal strength to preclude masking by anticipated ambient noise levels. Volume control settings for other signals should similarly preclude such masking. Ambient noise levels in hospital areas can range from 50 dB in a private room to 60 dB in intensive care units and emergency rooms, with peaks as high as 65 to 70 dB in operating rooms due to conversations, alarms, or the activation of other devices. The volume of monitoring signals normally should be lower than that of high-priority or medium-priority audible alarms provided on the same device. Audible signals should be located so as to assist the operator in identifying the device that is causing the alarm.

The use of voice alarms in medical applications should normally not be considered for the following reasons:

- Voice alarms are easily masked by ambient noise and other voice messages.
- Voice messages may interfere with communications among personnel who are attempting to address the alarm condition.
- The information conveyed by the voice alarm may reach individuals who should not be given specific information concerning the nature of the alarm.
- The types of messages transmitted by voice tend to be very specific, possibly causing complication and confusion to the user (and likely an awake patient!).
- In the situation where there are multiple alarms, multiple voice alarms would cause confusion.
- Different languages may be required to accommodate various markets.

The device's default alarm limits should be provided for critical alarms. These limits should be sufficiently wide to prevent nuisance alarms and sufficiently narrow to alert the operator to a situation that would be dangerous in the average patient. Generally speaking, the ability to mute alarms long term is not recommended (see following discussion).

The device may retain and store one or more sets of alarm limits (for example, adult or pediatric) chosen by the user. When more than one set of user default alarm limits exists, the activation of user default alarm limits should require deliberate action by the user. When there is only one set of user default alarm limits, the device may be configured to activate this set of user default alarm limits automatically in place of the factory default alarm limits.

The setting of adjustable alarms should be indicated continuously or on user demand. It should be possible to review alarm limits quickly. During user setting of alarm limits, monitoring should continue, and alarm conditions should elicit the appropriate alarms. Alarm limits may be set automatically or upon user action to reasonable ranges and/or percentages above and/or below existing values for monitored variables. Care should be used in the design of such automatic setting systems to help prevent nuisance alarms or variables that are changing within an acceptable range.

An audible high- or medium-priority signal may have a manually operated, temporary override mechanism that will silence it for a period of time, for example, 120 seconds. After the silencing

period, the alarm should begin sounding again if the alarm condition persists or if the condition was temporarily corrected but has now returned. New alarm conditions that develop during the silencing period should initiate audible and visual signals. If momentary silencing is provided, the silencing should be visually indicated.

An audible high- or medium-priority signal may be equipped with a means of permanent silencing, which may be appropriate when a continuous alarm is likely to degrade user performance of associated tasks to an unacceptable extent and in cases when users would otherwise be likely to disable the device altogether. If provided, such silencing should require that the user either confirm the intent to silence a critical life support alarm or take more than one step to turn the alarm off. Permanent silencing should be visually indicated and may be signaled by a periodic audible reminder. Permanent silencing of an alarm should not affect the visual representation of the alarm and should not disable the alarm.

Life support devices and devices that monitor a life-critical variable should have an audible alarm to indicate a loss of power or failure of the device. The characteristics of this alarm should be the same as those of the highest-priority alarm that becomes inoperative. It may be necessary to use battery power for such an alarm. Data logging, including alarms status, may also be a part of your design mandate.

9.14.10 Labeling

Controls, displays, and other equipment items that need to be located, identified, or manipulated should be appropriately and clearly marked to permit rapid and accurate human performance. The characteristics of markings should be determined by such factors as the criticality of the function labeled, the distance from which the labels have to be read, the illumination level, the colors, the time available for reading, the reading accuracy required, and consistency with other markings.

Receptacles and connectors should be marked with their intended function or their intended connection to a particular cable. Convenience receptacles should be labeled with maximum allowable load in amperes or watts. The current rating of fuses should be permanently marked adjacent to the fuse holder. Fuse ratings should be indicated either in whole number, common fractions, or whole number plus common fractions. Labeling of fuses and circuit breakers should be legible in the ambient illumination range anticipated for the maintainer's location.

Operators and maintenance personnel should be warned of possible fire, radiation, explosion, shock, infection, or other hazards that may be encountered during the use, handling, storage, or repair of the device. Electromedical instruments should be labeled to show whether they may be used in the presence of flammable gases or oxygen-rich atmospheres. Hazard warnings should be prominent and understandable.

Normally, labels should be placed above panel elements that users grasp, press, or otherwise handle so the label is not obscured by the hand. However, certain panel element positions, user postures, and handling methods may dictate other label placements. Labels should be positioned to ensure visibility and readability from the position in which they should be read.

Labels should be oriented horizontally so that they may be read quickly and easily from left to right. Although not normally recommended, vertical orientation may be used, but only where its use is justified in providing a better understanding of intended function. Vertical labels should be read from top to bottom. Curved labels should be avoided except when they provide setting delimiters for rotary controls.

Labels should not cover any other information source. They should not detract from or obscure figures or scales that should be read by the operator. Labels should not be covered or obscured by other units in the equipment assembly. Labels should be visible to the operator during control activation. All markings should be permanent and should remain legible throughout the life of the equipment under anticipated use and maintenance conditions.

The words employed in the label should express exactly what action is intended. Instructions should be clear and direct. Words that have a commonly accepted meaning for all intended users should be utilized. Unusual technical terms should be avoided. Labels should be consistent within and across pieces of equipment in their use of words, acronyms, abbreviations, and part/system numbers. No mismatch should exist between the nomenclature used in documentation and that printed on the labels.

Symbols should be used only if they have a commonly accepted meaning for all intended users. Symbols should be unique and distinguishable from one another. A commonly accepted standard configuration should be used.

Human factors engineering hardware design considerations should include functional dimensions, workstation architecture considerations, alarms and signals, and labeling, and should always take the operator's psychological characteristics into account.

9.14.11 Software

Computerized systems should provide a functional interface between the system and users of that system. This interface should be optimally compatible with the intended user and should minimize conditions that can degrade human performance or contribute to human error. Thus, procedures for similar or logically related transactions should be consistent. Every input by a user should consistently produce some perceptible response or output from the computer. Sufficient online help should be provided to allow the intended but uninitiated user to operate the device effectively in its basic functional mode without reference to a user's manual or experienced operator. Users should be provided appropriate information at all times on system status either automatically or upon request. Provision of information about system dysfunction is essential.

In applications where users need to log on to the system, log-on should be a separate procedure that should be completed before a user is required to select among any operational options. Appropriate prompts for log-on should be displayed automatically on the user's terminal with no special action required other than turning on the terminal. Users should be provided feedback relevant to the log-on procedure that indicates the status of the inputs. Log-on processes should require minimum input from the user, consistent with system access security.

In the event of a partial hardware/software failure, the program should allow for orderly shutdown and establishment of a checkpoint so restoration can be accomplished without loss of data.

Where two or more users need to have simultaneous access to a computer system, under normal circumstances, operation by one person should not interfere with the operations of another person. For circumstances in which certain operators require immediate access to the system, an organized system for insuring or avoiding preemption should be provided. Provisions should be made so that preempted users are notified and can resume operations at the point of interference without data loss.

9.14.12 Data Entry

Manual data entry functions should be designed to establish consistency of data entry transactions, minimize user's input actions and memory load, ensure compatibility of data entry with data display, and provide flexibility of user control of data entry. The system should provide feedback to the user about acceptance or rejection of an entry.

When a processing delay occurs, the system should acknowledge the data entry and provide the user with an indication of the delay. If possible, the system should advise the user of the time remaining for process completion.

Data entry should require an explicit completion action, such as the depression of an ENTER key to post an entry into memory. Data entries should be checked by the system for correct format,

acceptable value, or range of values. Where repetitive entry of data sets is required, data validation for each set should be completed before another transaction can begin.

Data should be entered in units that are familiar to the user. If several different systems of units are commonly used, the user should have the option of selecting the units either before or after data entry. Transposition of data from one system of units to another should be accomplished automatically by the device. When mnemonics or codes are used to shorten data entry, they should be distinctive and have a relationship or association to normal language or specific job-related terminology.

Data deletion or cancellation should require an explicit action, such as the depression of a DELETE key. When a data delete function has been selected by a user, a means of confirming the delete action should be provided, such as a dialogue box with a delete acknowledgment button or a response to a question such as "Are you sure? (Y/N)." In general, requiring a second press of the DELETE key is not preferred because of the possibility of an accidental double press. Similarly, after data have been entered, if the user fails to enter the data formally, for instance, by pressing an ENTER key, the data should not be deleted or discarded without confirmation from the user.

Deleted data should be maintained in a memory buffer from which they can be salvaged, such as the UNDELETE option. The size and accessibility of this buffer should depend on the value of the data that the user can delete from the system.

The user should always be given the opportunity to change a data entry after the data have been posted. When a user requests change or deletion of a data item that is not currently being displayed, the option of displaying the old value before confirming the change should be presented. Where a data archive is being created, the system should record both the original entry and all subsequent amendments.

9.14.13 Displays

Visual displays should provide the operator with a clear indication of equipment or system status under all conditions consistent with the intended use and maintenance of the system. The information displayed to a user should be sufficient to allow the user to perform the intended task but should be limited to what is necessary to perform the task or to make decisions. Information necessary for performing different activities, such as equipment operation versus troubleshooting, should not appear in a single display unless the activities are related and require the same information to be used simultaneously. Information should be displayed only within the limits of precision required for the intended user activity or decision making and within the limits of accuracy of the measure.

Graphic displays should be used for the display of information when perception of the pattern of variation is important to proper interpretation. The choice of a particular graphic display type can have significant impact on user performance. The designer should consider carefully the tasks to be supported by the display and the conditions under which the user will view the device before selecting a display type.

Numeric digital displays should be used where quantitative accuracy of individual data items is important. They should not be used as the only display of information when perception of the variation pattern is important to proper interpretation or when rapid or slow digital display rates inhibit proper perception.

Displays may be coded by various features, such as color, size, location, shape, or flashing lights. Coding techniques should be used to help discriminate among individual displays and to identify functionally related displays, the relationship among displays, and critical information within a display.

Display formats should be consistent within a system. When appropriate for users, the same format should be used for input and output. Data entry formats should match the source document formats. Essential data, text, and formats should be under computer, not user, control. When data fields have a naturally occurring order, such as chronological or sequential, such order should be reflected in the format organization of the fields. Where some displayed data items are of great significance, or require immediate user response, those items should be grouped and displayed prominently.

Separation of groups of information should be accomplished through the use of blanks, spacing, lines, color coding, or other similar means consistent with the application.

The content of displays within a system should be presented in a consistent, standardized manner. Information density should be held to a minimum in displays used for critical tasks. When a display contains too much data for presentation in a single frame, the data should be partitioned into separately displayable pages. The user should not have to rely on memory to interpret new data. Each data display should provide the needed context, including the recapitulation of prior data from prior displays, as necessary.

An appropriate pointing device, such as a mouse, trackball, or touch screen, should be used in conjunction with applications that are suited to direct manipulation, such as identifying landmarks on a scanned image or selecting graphical elements from a palette of options. The suitability of a given pointing device to user tasks should be assessed.

9.14.14 Interactive Control

General design objectives include consistency of control action, minimized need for control actions, and minimized memory load on the user, with flexibility of interactive control to adapt to different user needs. As a general principle, the user should decide what needs doing and when to do it. The selection of dialogue formats should be based on anticipated task requirements and user skills.

System response times should be consistent with operational requirements. Required user response times should be compatible with required system response time. Required user response times should be within the limits imposed by the total user task load expected in the operational environment.

Control–display relationships should be straightforward and explicit, as well as compatible with the lowest anticipated skill levels of users. Control actions should be simple and direct, whereas potentially destructive control actions should require focused user attention and command validation/confirmation before they are performed. Steps should be taken to prevent accidental use of destructive controls, including possible erasures or memory dump.

Feedback responses to correct user input should consist of changes in the state or value of those elements of the displays that are being controlled. These responses should be provided in an expected and logical manner. An acknowledgment message should be employed in those cases where the more conventional mechanism is not appropriate. Where control input errors are detected by the system, error messages and error recovery procedures should be available.

Menu selection can be used for interactive controls. Menu selection of commands is useful for tasks that involve the selection of a limited number of options or that can be listed in a menu, or in cases when users may have relatively little training. A menu command system that involves several layers can be useful when a command set is so large that users are unable to commit all the commands to memory and a reasonable hierarchy of commands exists for the user.

Form-filling interactive control may be used when some flexibility in data to be entered is needed and when the users will have moderate training. A form-filling dialogue should not be used when the computer has to handle multiple types of forms and computer response is slow.

Fixed-function key interactive control may be used for tasks requiring a limited number of control inputs or in conjunction with other dialogue types.

Command language interactive control may be used for tasks involving a wide range of user inputs and when user familiarity with the system can take advantage of the flexibility and speed of the control technique.

Question-and-answer dialogues should be considered for routine data entry tasks when data items are known and their ordering can be constrained, when users have little or no training, and when the computer is expected to have moderate response speed.

Query language dialogue should be used for tasks emphasizing unpredictable information retrieval with trained users. Query languages should reflect a data structure or organization perceived by the users to be natural.

Graphic interaction as a dialogue may be used to provide graphic aids as a supplement to other types of interactive control. Graphic menus may be used that display icons to represent the control options. This may be particularly valuable when system users have different linguistic backgrounds.

9.14.15 Feedback

Feedback should be provided that presents status, information, confirmation, and verification throughout the interaction. When system functioning requires the user to stand by, WAIT or similar-type messages should be displayed until interaction is again possible. When the standby or delay may last a significant period of time, the user should be informed. When a control process or sequence is completed or aborted by the system, a positive indication should be presented to the user about the outcome of the process and the requirements for subsequent user action. If the system rejects a user input, feedback should be provided to indicate why the input was rejected and the required corrective action.

Feedback should be self-explanatory. Users should not be made to translate feedback messages by using a reference system or code sheets. Abbreviations should not be used unless necessary.

9.14.16 Prompts

Prompts and help instructions should be used to explain commands, error messages, system capabilities, display formats, procedures, and sequences, as well as to provide data. When operating in special modes, the system should display the mode designation and the file(s) being processed. Before processing any user requests that would result in extensive or final changes to existing data, the system should require user confirmation. When missing data are detected, the system should prompt the user. When data entries or changes will be nullified by an abort action, the user should be requested to confirm the abort.

Neither humor nor admonishment should be used in structuring prompt messages. The dialogue should be strictly factual and informative. Error messages should appear as close as possible in time and space to the user entry that caused the message. If a user repeats an entry error, the second error message should be revised to include a noticeable change so that the user may be certain that the computer has processed the attempted correction.

Prompting messages should be displayed in a standardized area of the display. Prompts and help instructions for system-controlled dialogue should be clear and explicit. The user should not be required to memorize lengthy sequences or refer to secondary written procedural references.

9.14.17 Defaults

Manufacturer's default settings and configurations should be provided in order to reduce user workload. Currently defined default values should be displayed automatically in their appropriate data fields with the initiation of a data entry transaction. The user should indicate acceptance of the default values. Upon user request, manufacturers should provide a convenient means by which the user may restore factory default settings.

Users should have the option of setting their own default values for alarms and configurations on the basis of personal experience. A device may retain and store one or more sets of user default settings. Activation of these settings should require deliberate action by the user.

9.14.18 Data Correction

When users are required to make entries into a system, an easy means of correcting erroneous entries should be provided. The system should permit correction of individual errors without requiring reentry of correctly entered commands or data elements.

9.15 FITTS'S LAW

Fitts's law is a model of human movement that predicts the time required to rapidly move to a target area, as a function of the distance to the target and the size of the target. Fitts's law is used to model the act of pointing, both in the real world, for example, with a hand or finger, and on computers, for example, with a mouse. It was published in 1954 by Paul Fitts.[1]

Theoretically, the following principles exist when applying Fitts's law to interface designs:

- Things done more often should be assigned a larger button.
- Things done more often should be closer to the average position of the user's cursor.
- The top, bottom, and sides of the screen are more easily targeted because of the boundary created by the edges of the screen.

9.15.1 The Model

Mathematically, Fitts's law has been formulated in several different ways. One common form is the Shannon formulation for movement in a single dimension:

$$T = a + b \log_2 (D/W + 1)$$

where

T	the average time taken to complete the movement
a	the start/stop time of the device
b	the inherent speed of the device
D	the distance from the starting point to the center of the target
W	the width of the target measured along the axis of motion

From the equation, we can see a speed–accuracy tradeoff associated with pointing, whereby targets that are smaller and/or further away require more time to acquire.

Fitts's law is an unusually successful and well-studied model. Experiments that reproduce Fitts's law and/or that demonstrate the applicability of Fitts's law in somewhat different situations are not difficult to perform. The measured data in such experiments often fit a straight line with a correlation coefficient of 0.95 or higher, a sign that the model is very accurate.

Since the advent of graphical user interfaces, Fitts's law has been applied to tasks where the user must position the mouse cursor over an on-screen target, such as a button or other widget. Fitts's law can model both point-and-click and drag-and-drop actions. As a result of this law, there are some consequences for user interface design, including the following:

- Buttons and other graphical user interface controls should be a reasonable size, as it is difficult to click on small ones.
- Edges and corners of the computer display are particularly easy to acquire because the pointer remains at the screen edge regardless of how much further the mouse is moved.
- Pop-up menus can usually be opened faster than pull-down menus, as the user avoids large excursion of the finger (or other "pointer" device).
- Pie menu items typically are selected faster and have a lower error rate than linear menu items because (1) pie menu items are all at the same small distance from the center of the menu, and (2) their wedged-shaped target areas are very large.

Another prevalent use of Fitts's law is to help study and compare input devices. It has been verified to be able to predict user performance in some common tasks, such as point-select and point-drag tasks, using common input devices, such as a mouse, trackball, or stylus. A study of hand and

head movements in two dimensions by Jagacinski and Monk (1985)[2] found that Fitts's law also described head movement, and it worked for two dimensions with angular uncertainty.

EXERCISES

1. Do a web search on the author Jeff(rey) Cooper, and isolate the papers referring to mishaps. Locate and report on one of his human factors papers relevant to anesthesia.
2. Visit the American National Standards Institute (ANSI) website (www.ansi.org); search for the number of standards relating to "color," "alarms," "human factors," and "labeling." Comment on your results.
3. Observe the layout of controls on your car, versus the layout of controls on a different brand. Where and why are there differences?
4. There has been a significant trend in using "internationally recognized" symbols rather than text to denote controls. Find and report on one example in your environment.
5. Discuss the differences in expectations for medical devices such as dialysis equipment to be used in the home versus in a clinic.
6. Discuss the differences in expectations for blood pressure determination in the home versus in the clinic.
7. Do a web search to locate ergonomic data. Why are designs generally aimed at the 5% female to 95% male ranges?
8. Do a web search for front panel web simulator software; report on your results. Find an example of a car dashboard layout.
9. Prototype a front panel layout for display of pulse oximeter data for joggers.
10. How would you redesign an operating room for a deaf anesthesiologist?
11. What branches of medicine are available for a blind physician? Why?
12. Given a large 1600 × 1200 screen, where should a target be placed so that the user can access it the fastest, no matter where the user is originally located?

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10 Industrial Design

> The future of the aircraft industry is still the responsibility of the engineer. Money alone never did and never will create anything.
>
> ***Aviation Magazine* (now *Aviation Week*)**

Industrial design is the professional service of creating and developing concepts and specifications that optimize the function, value, and appearance of products and systems for the mutual benefit of both user and manufacturer. Industrial designers develop these concepts and specifications through collection, analysis, and synthesis of data guided by the special requirements of the client or manufacturer. They are trained to prepare clear and concise recommendations through drawings, models, and verbal descriptions. Industrial design services are often provided within the context of cooperative working relationships with other members of a development group. Typical groups include management, marketing, engineering, and manufacturing specialists. The industrial designer expresses concepts that embody all relevant design criteria determined by the group.

The industrial designer's unique contribution places emphasis on those aspects of the product or system that relate most directly to human characteristics, needs, and interests. This contribution requires specialized understanding of visual, tactile, safety, and convenience criteria, with concern for the user. Education and experience in anticipating psychological, physiological, and sociological factors that influence and are perceived by the user are essential industrial design resources. Industrial designers also maintain a practical concern for technical processes and requirements for manufacture; marketing opportunities and economic constraints; and distribution, sales, and servicing processes. They work to ensure that design recommendations use materials and technology effectively and comply with all legal and regulatory requirements.

In addition to supplying concepts for products and systems, industrial designers are often retained for consultation on a variety of problems that have to do with a client's image. Such assignments include product and organization identity systems, development of communication systems, interior space planning and exhibit design, advertising devices and packaging, and other related services. Their expertise is sought in a wide variety of administrative arenas to assist in developing industrial standards, regulatory guidelines, and quality control procedures to improve manufacturing operations and products. Industrial designers, as professionals, are guided by their awareness of obligations to fulfill contractual responsibilities to clients, to protect the public safety and well-being, to respect the environment, and to observe ethical business practice.

The term *industrial design* was coined early in the 20th century to describe for mass-produced devices the creative role previously performed by an individual artisan. In keeping with the complexity of mass production, industrial designers work with other professions involved in conceiving, developing, and manufacturing products, including the following:

- Marketing experts
- Design engineers
- Biomedical engineers
- Human factors specialists
- Manufacturing engineers
- Service personnel

Together with human factors specialists, industrial designers conduct usability studies to ensure that a product meets the user's needs, wants, and expectations. They often rearrange internal components to make products more efficient to manufacture and easy to assemble, service, and recycle.

As about one-third of all medical device incident reports involve use error, the need for improved interfaces between devices and users is evident.

10.1 SET USABILITY GOALS

Usability goals are comparable to other types of engineering goals in the sense that they are quantitative and provide a basis for acceptance testing. Goals may be objective or subjective. A sample objective goal might be as follows: "On average, users shall require 3 seconds to silence an alarm." This goal is an objective goal because the user's performance level can be determined simply by observation. For example, you can use a stopwatch to determine task times. Other kinds of objective goals concentrate on the number of user errors and the rate of successful task completion.

A sample subjective goal is as follows: "On average, 75% of users shall rate the intuitiveness of the alarm system as 5 or better, where 1 = poor and 7 = excellent." The range 1–7 (or other) is a Likert scale, which is a form of "psychometric" response scale often used to evaluate such items as usability and professors' lecture skills. This goal is subjective because it requires asking the user's opinion about their interaction with the given product. A rating sheet can be used to record their answers. Other kinds of subjective goals concentrate on mental processing and emotional response attributes, such as learning, frustration level, fear of making mistakes, and so forth.

Every usability goal is based on a usability attribute, for example, task, speed, or intuitiveness; includes a metric such as time or scale; and sets a target performance level, such as 3 seconds or a rating of 5 or better.

Typically, up to 50 usability goals may be written for a given project, two-thirds of which are objective and one-third of which are subjective. The target performance level on each goal is based on findings from preceding user studies, particularly the benchmark usability testing. If there is no basis for comparison, that is, there are no comparable products, then engineering judgment must be used to set the initial goals and adjust them as necessary to assure they are realistic.

10.2 DESIGN USER INTERFACE CONCEPTS

Concurrent design is a productive method of developing a final user interface design. It enables the thorough exploration of several design concepts before converging on a final solution. In the course of exploring alternative designs, limited prototypes should be built of the most promising concepts and user feedback obtained on them. This gets users involved in the design process at its early stages and assures that the final design will be closely matched to users' expectations.

Note that the design process steps described following assume that the product includes both hardware and software elements. Some steps would be moot if the product had no software user interface.

10.2.1 Develop Conceptual Model

When users interact with a product, they develop a mental model of how it works. This mental model may be complete and accurate or just the opposite. Enabling the user to develop a complete and accurate mental model of how a product works is a challenge. The first step is developing so-called conceptual models of how to represent the product's functions. This exercise provides a terrific opportunity for design innovation. The conceptual model may be expressed as a bubble diagram, for example, that illustrates the major functions of the product and functional interrelationships as

you would like the users to think of them. You can augment the bubble diagram with a narrative description of the conceptual model.

10.2.2 Develop User Interface Structure

Develop alternative user interface structures that complement the most promising two to three conceptual models. These structures can be expressed in the form of screen hierarchy maps that illustrate where product functions reside and how many steps it will take users to get to them. Such maps may take the form of a single element, a linear sequence, a tree structure (cyclic or acyclic), or a network. In addition to software screens, such maps should show which functions are allocated to dedicated hardware controls.

10.2.3 Define Interaction Style

In conjunction with the development of the user interface structures, alternative interaction styles should be defined. Possible styles include question-and-answer dialogs, command lines, menus, and direct manipulation.

10.2.4 Develop Screen Templates

Determine an appropriate size of display based on the user interface structure and interaction style, as well as other engineering considerations. Using computer-based drawing tools, draw the outline of a blank screen. Next, develop a limited number (perhaps three to five) of basic layouts for the information that will appear on the various screens. Normally, it is best to align all elements, such as titles, windows, prompts, and numerics, according to a grid system.

10.2.5 Develop Hardware Layout

Apply established design principles in the development of hardware layouts that are compatible with the evolving software user interface solutions. Assure that the layouts reinforce the overall conceptual model.

10.2.6 Develop a Screenplay

Apply established design principles in the development of a detailed screenplay. Do not bother to develop every possible screen at this time. Rather, develop only those screens that would enable users to perform frequently used, critical, and particularly complex functions. Base the screen designs on the templates. Create new templates or eliminate existing templates as required while continuing to limit the total number of templates. Assure that the individual screens reinforce the overall conceptual model. You may choose to get user feedback on the screenplay (what some people call a paper prototype). You may show your coworkers the paper concept and then ask them to "control the system" while giving you oral feedback on their thoughts during the process.

10.2.7 Develop a Refined Design

Developing a hardware layout and developing a screenplay describe prototyping and testing the user interface. These efforts will help determine the most promising design concept or suggest a hybrid of two or more concepts. The next step is to refine the preferred design. Several reiterations of the preceding steps may be necessary, including developing a refined conceptual model, developing a refined user interface structure, and developing an updated set of screen templates. Then, a refined screenplay and hardware layout may be developed.

10.2.8 Develop a Final Design

The steps listed in 10.2.5 and 10.2.6 describe prototyping and testing the user interface. These efforts will help you determine any remaining usability problems with the refined design and opportunities for further improvement. It is likely that design changes at this point will be limited in nature. Most can be made directly to the prototype.

10.3 MODEL THE USER INTERFACE

Build a prototype to evaluate the dynamics of the user interface. Early prototypes of competing concepts may be somewhat limited in terms of their visual realism and how many functions they perform. Normally, it is best to develop a prototype that (1) presents a fully functional top level that allows users to browse their basic options, and (2) enables users to perform a few sample tasks, that is, walk through a few scenarios. As much as possible, include tasks that relate to the established usability goals.

User interface prototypes may be developed using conventional programming languages or rapid prototyping languages, such as SuperCard, Altia Design, Visual Basic, Toolbook, and the like. The rapid prototyping languages are generally preferable because they allow for faster prototyping and are easier to modify based on core project team and user feedback. If possible, the use of a touch screen system should be implemented at this stage, along with testing of the interfaces again by your coworkers. If none of you are frustrated at the end of a testing session, you have likely done a reasonable job on the design so far. An additional advantage at this point is that some of the actions, such as response time to an alarm, may now be documented with your software.

Page layouts may even be mocked up in your computer editing software, for example, with Microsoft Word. Figure 10.1 is a rendition of a computer control scheme that author King used in the development of a computerized anesthesia monitoring system.

Early in the screenplay development process, it may make sense to prototype a small part of the user interface to assess design alternatives or to conduct limited studies, such as how frequently to flash a warning. Once detailed screenplays of competing concepts are available, build higher-fidelity prototypes that facilitate usability testing. Once a refined design is developed, build a fully functional prototype that permits a verification usability test. Such prototypes can be refined based on final test results and serve as a specification.

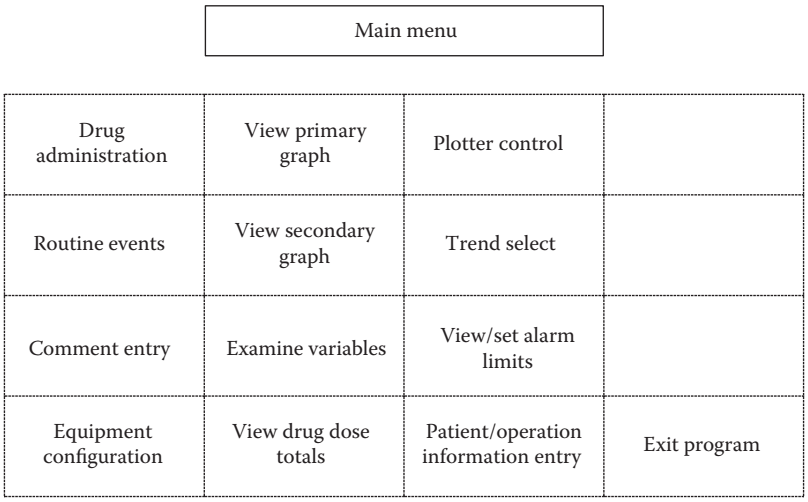

FIGURE 10.1 Mockup of a touch screen control screen.

10.4 TEST THE USER INTERFACE

There are several appropriate times to conduct a usability test, including the following:

- At the start of a development effort to develop benchmarks
- When you have paper-based or computer-based prototypes of competing design concepts
- When you have a prototype of your refined design
- When you want to develop marketing claims regarding the performance of the actual product

While the rigor of the usability test may change, based on the timing of the test, the basic approach remains the same. You recruit prospective users to spend a concentrated period of time interacting with the prototype product. The users may undertake a self-exploration or perform directed tasks. During the course of such interactions, you note the test participants' comments and document their performance. At intermittent stages, you may choose to have the test participant complete a questionnaire or rating/ranking exercise. Videotaping test proceedings is one way to give those unable to attend the test a first-hand sense of user–product interactions. Sometimes, it is useful to create a 10- to 15-minute highlight tape that shows the most interesting moments of all test sessions.

During testing, collect the data necessary to determine if you are meeting the established usability goals. This effort will add continuity and objectivity to the usability engineering process.

10.5 SPECIFY THE USER INTERFACE

10.5.1 Style Guide

The purpose of a style guide is to document the rules of the user interface design. By establishing such rules, you can check the evolving design to determine any inconsistencies. Also, it assures the consistency of future design changes. Style guides, usually 10–15 pages in length, normally include a description of the conceptual model, the design elements, and elements of style.

10.5.2 Screen Hierarchy Map

The purpose of a screen hierarchy map is to provide an overview of the user interface structure. It places all screens that appear in the screenplay in context. It enables the flow of activity to be studied in order to determine if it reinforces the conceptual model. It also helps to determine how many steps users will need to take to accomplish a given task. Graphical elements of the screen hierarchy map should be cross-indexed to the screenplay.

10.5.3 Screenplay

The purpose of a screenplay is to document the appearance of all major screens on paper. Typically, screen images are taken directly from the computer-based prototype. Ideally, the screenplay should present screen images in their actual scale and resolution. Each screen should be cross-indexed to the screen hierarchy map.

10.5.4 Specification Prototype

The purpose of the specification prototype is to model accurately the majority of user interface interactions. This provides the core project team with a common basis for understanding how the final product should work. It provides a basis for writing the user documentation. It may also be used to orient those involved in marketing, sales, and training.

10.5.5 Hardware Layouts

The hardware layout may be illustrated by the specification prototype. However, the hardware may not be located proximal to the software user interface. If this is the case, develop layout drawings to document the final hardware layout.

10.6 ADDITIONAL INDUSTRIAL DESIGN CONSIDERATIONS

The design of medical devices should reflect industrial design features that increase the potential for successful performance of tasks and for satisfaction of design objectives.

10.6.1 Consistency and Simplicity

Where common functions are involved, consistency is encouraged in controls, displays, markings, coding, and arrangement schemes for consoles and instrument panels.

Simplicity in all designs is encouraged. Equipment should be designed to be operated, maintained, and repaired in its operational environment by personnel with appropriate but minimal training. Unnecessary or cumbersome operations should be avoided when simpler, more efficient alternatives are available.

10.6.2 Safety

Medical device design should reflect system and personnel safety factors, including the elimination or minimization of the potential for human error during operation and maintenance under both routine and nonroutine or emergency conditions. Machines should be designed to minimize consequence of human error. For example, where appropriate, a design should incorporate redundant, diverse elements arranged in a manner that increases overall reliability when failure can result in the inability to perform a critical function.

Any medical device failure should immediately be indicated to the operator and should not adversely affect safe operation of the device. Where failures can affect safe operation, simple means and procedures for averting adverse effects should be provided.

When the device failure is life threatening or could mask a life-threatening condition, an audible alarm and a visual display should be provided to indicate the device failure. Wherever possible, explicit notification of the source of failure should be provided to the user. Concise instructions on how to return to operation or how to invoke alternate backup methods should be provided.

The reader should consider two other overriding factors at this point. First, if the device can be made "fail-safe," it should be done. This implies that despite a failure in the device, the essential functions of the device, such as delivery of oxygen, are not compromised. Second, it is mandated in the design of medical devices that safety considerations be considered; thus, this interface design development will be one of the areas that must be documented.

10.6.3 Environmental/Organizational Considerations

The design of medical devices should consider the following:

- The levels of noise, vibration, humidity, and heat that will be generated by the device and the levels of noise, vibration, humidity, and heat to which the device and its operators and maintainers will be exposed in the anticipated operational environment
- The need for protecting operators and patients from electric shock, thermal, infectious, toxicologic, radiologic, electromagnetic, visual, and explosion risks, as well as from potential design hazards, such as sharp edges and corners, and the danger of the device falling on the patient or operator

- The adequacy of the physical, visual, auditory, and other communication links among personnel and between personnel and equipment
- The importance of minimizing psychophysiological stress and fatigue in the clinical environment in which the medical device will be used
- The impact on operator effectiveness of the arrangement of controls, displays, and markings on consoles and panels, and the potential effects of natural or artificial illumination used in the operation, control, and maintenance of the device
- The need for rapid, safe, simple, and economical maintenance and repair
- The possible positions of the device in relation to the users as a function of the user's location and mobility
- The electromagnetic environment(s) in which the device is intended to be used

10.6.4 Documentation

Documentation is a general term that includes operator manuals, instruction sheets, online help systems, and maintenance manuals. These materials may be accessed by many types of users. Therefore, the documentation should be written to meet the needs of all target populations.

Preparation of instructional documentation should begin as soon as possible during the specification phase. This assists device designers in identifying critical human factors and engineering needs and in producing a consistent human interface. The device and its documentation should be developed together.

During the planning phase, a study should be made of the capabilities and information needs of the documentation users, including the following:

- The user's mental abilities
- The user's physical abilities
- The user's previous experience with similar devices
- The user's general understanding of the general principles of operation and potential hazards associated with the technology
- The special needs or restrictions of the environment

As a minimum, the operator's manual should include detailed procedures for setup, normal operation, emergency operation, cleaning, and operator troubleshooting.

The operator manual should be tested on models of the device. It is important that these test populations be truly representative of end users and that they not have advance knowledge of the device.

Maintenance documentation should be tested on devices that resemble production units.

Documentation content should be presented in language free of vague and ambiguous terms. The simplest words and phrases that convey the intended meaning should be used. Terminology within the publication should be used. Use of abbreviations should be kept to a minimum but defined where they are used. Programs exist that estimate the "grade level" of a particular document; some estimate that most documentation should be developed using an average of eighth-grade vocabulary.

Information included in warnings and cautions should be chosen carefully and with consideration of the skills and training of intended users. It is especially important to inform users about unusual hazards and hazards specific to the device.

Human factors engineering design features should assure that the device functions consistently, simply, and safely, and that the environment, system organization, and documentation are analyzed and considered in the design, thus increasing the potential for successful performance of tasks and for satisfaction of design objectives.

10.6.5 Alarms and Signals

The purpose of an alarm is to draw attention to the device when the operator's attention may be focused elsewhere. Alarms should not be startling but should elicit the desired action from the user. When appropriate, the alarm message should provide instructions for the corrective action that is required. In general, alarm design will be different for a device that is continuously attended by a trained operator, such as an anesthesia machine, than for a device that is unattended and operated by an untrained operator, such as a patient-controlled analgesia device. False alarms, loud and startling alarms, or alarms that recur unnecessarily can be a source of distraction for both an attendant and the patient and thus be a hindrance to good patient care. Two cautions: First, the shutting off of alarms has resulted in more than one death. Second, the requirement (on some systems) that a patient be "admitted" (or similar terminology) has also led to patient deaths as the system was not programmed to alarm unless a condition was set.

Alarm characteristics are grouped into the following three categories:

1. High priority: a combination of audible and visual signals indicating that immediate operator response is required
2. Medium priority: a combination of audible and visual signals indicating that prompt operator response is required
3. Low priority: a visual signal or a combination of audible and visual signals indicating that operator awareness is required

A red flashing light should be used for a high-priority alarm condition unless an alternative visible signal that indicates the alarm condition and its priority is employed. A red flashing light should not be used for any other purpose.

A yellow flashing light should be used for a medium-priority alarm condition unless an alternative visible signal that indicates the alarm condition and its priority is employed. A yellow flashing light should not be used for any other purpose.

A steady yellow light should be used for a low-priority alarm condition unless an alternative visible signal that indicates the alarm condition and its priority is employed.

Audible signals should be used to alert the operator to the status of the patient or the device when the device is out of the operator's line of sight. Audible signals used in conjunction with visual displays should be supplementary to the visual signals and should be used to alert and direct the user's attention to the appropriate visual display.

Design of equipment should take into account the background noise and other audible signals and alarms that will likely be present during the intended use of the device. The lowest volume control settings of the critical life support audible alarms should provide sufficient signal strength to preclude masking by anticipated ambient noise levels. Volume control settings for other signals should similarly preclude such masking. Ambient noise levels in hospital areas can range from 50 dB in a private room to 60 dB in intensive care units and emergency rooms, with peaks as high as 65 to 70 dB in operating rooms due to conversations, alarms, or the activation of other devices. The volume of monitoring signals normally should be lower than that of high-priority or medium-priority audible alarms provided on the same device. Audible and visual signals should be located so as to assist the operator in identifying the device that is causing the alarm. Audible alarms also should not be able to be physically blocked from alarming (such as by a pillow, etc.).

The use of voice alarms in medical applications should normally not be considered for the following reasons:

- Voice alarms are easily masked by ambient noise and other voice messages.
- VOICE messages may interfere with communications among personnel who are attempting to address the alarm condition.

- The information conveyed by the voice alarm may reach individuals who should not be given specific information concerning the nature of the alarm (such as the patient!).
- The types of messages transmitted by voice tend to be very specific, possibly causing complication and confusion to the user.
- In the situations where there are multiple alarms, multiple voice alarms would cause confusion.
- Different languages may be required to accommodate various markets.

The device's default alarm limits should be provided for critical alarms. These limits should be sufficiently wide to prevent nuisance alarms and sufficiently narrow to alert the operator to a situation that would be dangerous in the average patient.

The device may retain and store one or more sets of alarm limits chosen by the user. When more than one set of user default alarm limits exists, the activation of user default alarm limits should require deliberate action by the user. When there is only one set of user default alarm limits, the device may be configured to activate this set of user default alarm limits automatically in place of the factory default alarm limits.

The setting of adjustable alarms should be indicated continuously or on user demand. It should be possible to review alarm limits quickly. During user setting of alarm limits, monitoring should continue, and alarm conditions should elicit the appropriate alarms. Alarm limits may be set automatically or upon user action to reasonable ranges and/or percentages above and/or below existing values for monitored variables. Care should be used in the design of such automatic setting systems to help prevent nuisance alarms or variables that are changing within an acceptable range.

An audible high- or medium-priority signal may have a manually operated, temporary override mechanism that will silence it for a period of time, for example, 120 seconds. After the silencing period, the alarm should begin sounding again if the alarm condition persists or if the condition was temporarily corrected but has now returned. New alarm conditions that develop during the silencing period should initiate audible and visual signals. If momentary silencing is provided, the silencing should be visually indicated.

An audible high- or medium-priority signal may be equipped with a means of permanent silencing, which may be appropriate when a continuous alarm is likely to degrade user performance of associated tasks to an unacceptable extent and in cases when users would otherwise be likely to disable the device altogether. If provided, such silencing should require that the user either confirm the intent to silence a critical life support alarm or take more than one step to turn the alarm off. Permanent silencing should be visually indicated and may be signaled by a periodic audible reminder. Permanent silencing of an alarm should not affect the visual representation of the alarm and should not disable the alarm.

Life support devices and devices that monitor a life-critical variable should have an audible alarm to indicate a loss of power or failure of the device. The characteristics of this alarm should be the same as those of the highest-priority alarm that becomes inoperative. It may be necessary to use battery power for such an alarm. Some consideration (generally not the industrial designer's job) should be given to the use of computer memory to document machine and patient status during and near alarm conditions. Such a recording can be of value in debugging systems and may be of value legally in the case of a death or injury.

10.6.6 Displays

Visual displays should provide the operator with a clear indication of equipment or system status under all conditions consistent with the intended use and maintenance of the system. The information displayed to a user should be sufficient to allow the user to perform the intended task but should be limited to what is necessary to perform the task or to make decisions. Information necessary for performing different activities, such as equipment operation versus troubleshooting, should not

appear in a single display unless the activities are related and require the same information to be used simultaneously. Information should be displayed only within the limits of precision required for the intended user activity or decision making and within the limits of accuracy of the measure.

Graphic displays should be used for the display of information when perception of the pattern of variation is important to proper interpretation. The choice of a particular graphic display type can have significant impact on user performance. The designer should consider carefully the tasks to be supported by the display and the conditions under which the user will view the device, before selecting a display type.

Numeric digital displays should be used where quantitative accuracy of individual data items is important. They should not be used as the only display of information when perception of the variation pattern is important to proper interpretation or when rapid or slow digital display rates inhibit proper perception. They should generally display only a consistent and honest number of significant figures.

Displays may be coded by various features, such as color, size, location, shape, or flashing lights. Coding techniques should be used to help discriminate among individual displays and to identify functionally related displays, the relationship among displays, and critical information within a display.

Display formats should be consistent within a system. When appropriate for users, the same format should be used for input and output. Data entry formats should match the source document formats. Essential data, text, and formats should be under computer, not user, control. When data fields have a naturally occurring order, such as chronological or sequential, such order should be reflected in the format organization of the fields. Where some displayed data items are of great significance, or require immediate user response, those items should be grouped and displayed prominently. Separation of groups of information should be accomplished through the use of blanks, spacing, lines, color coding, or other similar means consistent with the application.

The content of displays within a system should be presented in a consistent, standardized manner. Information density should be held to a minimum in displays used for critical tasks. When a display contains too much data for presentation in a single frame, the data should be partitioned into separately displayable pages. The user should not have to rely on memory to interpret new data. Each data display should provide the needed context, including the recapitulation of prior data from prior displays, as necessary.

An appropriate pointing device, such as a mouse, trackball, or touch screen, should be used in conjunction with applications that are suited to direct manipulation, such as identifying landmarks on a scanned image or selecting graphical elements from a palette of options. The suitability of a given pointing device to user tasks should be assessed. Consideration should also be given to the potential need for a backup input device.

10.6.7 Interactive Control

General design objectives include consistency of control action, minimized need for control actions, and minimized memory load on the user, with flexibility of interactive control to adapt to different user needs. As a general principle, the user should decide what needs doing and when to do it. The selection of dialogue formats should be based on anticipated task requirements and user skills.

System response times should be consistent with operational requirements. Required user response times should be compatible with required system response time. Required user response times should be within the limits imposed by the total user task load expected in the operational environment.

Control–display relationships should be straightforward and explicit, as well as compatible with the lowest anticipated skill levels of users. Control actions should be simple and direct, whereas potentially destructive control actions should require focused user attention and command validation/confirmation before they are performed. Steps should be taken to prevent accidental use of destructive controls, including possible erasures or memory dump.

Feedback responses to correct user input should consist of changes in the state or value of those elements of the displays that are being controlled. These responses should be provided in an

expected and logical manner. An acknowledgment message should be employed in those cases where the more conventional mechanism is not appropriate. Where control input errors are detected by the system, error messages and error recovery procedures should be available.

Menu selection can be used for interactive controls. Menu selection of commands is useful for tasks that involve the selection of a limited number of options or that can be listed in a menu, or in cases when users may have relatively little training. A menu command system that involves several layers can be useful when a command set is so large that users are unable to commit all the commands to memory and a reasonable hierarchy of commands exists for the user.

Form-filling interactive control may be used when some flexibility in data to be entered is needed and when the users have moderate training. A form-filling dialogue should not be used when the computer has to handle multiple types of forms and computer response is slow.

Fixed-function key interactive control may be used for tasks requiring a limited number of control inputs or in conjunction with other dialogue types.

Command language interactive control may be used for tasks involving a wide range of user inputs and when user familiarity with the system can take advantage of the flexibility and speed of the control technique.

Question-and-answer dialogues should be considered for routine data entry tasks when data items are known and their ordering can be constrained, when users have little or no training, and when the computer is expected to have moderate response speed.

Query language dialogue should be used for tasks emphasizing unpredictable information retrieval with trained users. Query languages should reflect a data structure or organization perceived by the users to be natural.

Graphic interaction as a dialogue may be used to provide graphic aids as a supplement to other types of interactive control. Graphic menus may be used that display icons to represent the control options. This may be particularly valuable when system users have different linguistic backgrounds.

10.6.8 Software

Computerized systems should provide a functional interface between the system and users of that system. This interface should be optimally compatible with the intended user and should minimize conditions that can degrade human performance or contribute to human error. Thus, procedures for similar or logically related transactions should be consistent. Every input by a user should consistently produce some perceptible response or output from the computer. Sufficient online help should be provided to allow the intended but uninitiated user to operate the device effectively in its basic functional mode without reference to a user's manual or experienced operator. Users should be provided appropriate information at all times on system status either automatically or upon request. Provision of information about system dysfunction is essential.

In applications where users need to log on to the system, log-on should be a separate procedure that should be completed before a user is required to select among any operational options. Appropriate prompts for log-on should be displayed automatically on the user's terminal with no special action required other than turning on the terminal. Users should be provided feedback relevant to the log-on procedure that indicates the status of the inputs. Log-on processes should require minimum input from the user, consistent with system access security.

In the event of a partial hardware/software failure, the program should allow for orderly shutdown and establishment of a checkpoint so restoration can be accomplished without loss of data.

Where two or more users need to have simultaneous access to a computer system, under normal circumstances, operation by one person should not interfere with the operations of another person. For circumstances in which certain operators require immediate access to the system, an organized system for insuring against or avoiding preemption should be provided. Provisions should be made so that preempted users are notified and can resume operations at the point of interference without data loss.

10.6.9 Data Entry

Manual data entry functions should be designed to establish consistency of data entry transactions, minimize a user's input actions and memory load, ensure compatibility of data entry with data display, and provide flexibility of user control of data entry. The system should provide feedback to the user about acceptance or rejection of an entry.

When a processing delay occurs, the system should acknowledge the data entry and provide the user with an indication of the delay. If possible, the system should advise the user of the time remaining for process completion. Data entry should require an explicit completion action, such as the depression of an ENTER key to post an entry into memory. Data entries should be checked by the system for correct format, acceptable value, or range of values. Where repetitive entry of data sets is required, data validation for each set should be completed before another transaction can begin.

Data should be entered in units that are familiar to the user. If several different systems of units are commonly used, the user should have the option of selecting the units either before or after data entry. Transposition of data from one system of units to another should be accomplished automatically by the device. When mnemonics or codes are used to shorten data entry, they should be distinctive and have a relationship or association to normal language or specific job-related terminology.

Data deletion or cancellation should require an explicit action, such as the depression of a DELETE key. When a data delete function has been selected by a user, a means of confirming the delete action should be provided, such as a dialogue box with a delete acknowledgment button or a response to a question such as "Are you sure? (Y/N)." In general, requiring a second press of the DELETE key is not preferred because of the possibility of an accidental double press. Similarly, after data have been entered, if the user fails to enter the data formally, for instance, by pressing an ENTER key, the data should not be deleted or discarded without confirmation from the user.

Deleted data should be maintained in a memory buffer from which they can be salvaged, such as the UNDELETE option. The size and accessibility of this buffer should depend on the value of the data that the user can delete from the system.

The user should always be given the opportunity to change a data entry after the data have been posted. When a user requests change or deletion of a data item that is not currently being displayed, the option of displaying the old value before confirming the change should be presented. Where a data archive is being created, the system should record both the original entry and all subsequent amendments.

10.6.10 Feedback

Feedback should be provided that presents status, information, confirmation, and verification throughout the interaction. When system functioning requires the user to standby, a WAIT or similar type of message should be displayed until interaction is again possible. When the standby or delay may last a significant period of time, the user should be informed. When a control process or sequence is completed or aborted by the system, a positive indication should be presented to the user about the outcome of the process and the requirements for subsequent user action. If the system rejects a user input, feedback should be provided to indicate why the input was rejected and the required corrective action.

Feedback should be self-explanatory. Users should not be made to translate feedback messages by using a reference system or code sheets. Abbreviations should not be used unless necessary.

10.6.11 Error Management/Data Protection

When users are required to make entries into a system, an easy means of correcting erroneous entries should be provided. The system should permit correction of individual errors without requiring reentry of correctly entered commands or data elements.

10.7 EXAMPLES

10.7.1 Initial Presentation to a User

A company has an idea for a new device containing several modules. Some modules have computer screens where the user may interface with the device. The company wants to bring the idea to typical users of the device to determine the best fit for the various modules. The designers make simulated modules out of cardboard or wood such that they may be interchangeable on the device. Those modules with screens for interfacing have screens drawn on them with black marker. The set of modules is then brought to various users and set up as the company thinks they should be. The users are then asked to look at the device, pretend they are using it in a procedure, and move modules to their optimum position for their use. Any changes to the orientation of the modules is recorded along with the user information, and the device is taken to the next user. After accumulating sufficient user input, the company makes a decision on the optimum position of the modules, all based on user input.

10.7.2 Conducting User Task Studies

A company has developed a working prototype of a new device, based on user input. The company now wants to determine if the design is optimum for typical usage. Users are brought to a room containing the working prototype and given a series of tasks to perform on the device. The device is located in a room containing a one-way mirror, so that designers can observe the users without interfering with their tasks. The engineers have stopwatches to determine the length of time it takes the user to complete each task. Users are also asked to document any problems or concerns they have while completing the task. This information is accumulated for a group of users and fed back to the design team to determine if and where improvements to the design can be made.

EXERCISES

1. Compare the work done by persons concerned primarily with human factors (Chapter 8) to the work done by industrial designers (this chapter).
2. Perform a web search using the search term “industrial design.” Summarize the results from your first 10 hits.
3. Visit the website for the Industrial Design Society of America (idsa.org). Find and report on their definition of industrial design.
4. Visit the website devicelink.com; go to one of the expos listed (such as MD&M West). Search for the listing for contract manufacturers. Of the first 10 or so, how many would qualify as industrial designers (list and discuss).
5. Do a web search for front panel web simulator software; report on your results. Find an example of a medical device panel layout.
6. Prototype a front panel layout for display of exercise data for a weight watchers clinic.
7. Your company wants to present a new design to a select group of doctors at a medical convention. The device will be shown to the doctors individually in a room separate from the convention. As one of the design engineers, what steps would you take to prepare the device for the showing?
8. You are a software developer who has just completed a program for calculating drug dosages based on patient medical records. One of the marketing people wants to take a copy of the program to a customer for their initial evaluation. What steps need to be taken to ensure protection of this beta copy and to reduce the risk of liability to the company?
9. Which of the 11 problems in Chapter 8 may also apply to this chapter, and why?

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11 Biomaterials and Material Testing

> Developing products to be implanted and to function inside the highly intricate environment of the human body is among the most complex and challenging of all the academic and business pursuits in bioengineering.
>
> **Lory A. Frenkel**

Biomaterials is a wide-ranging field, encompassing aspects of basic biology, medicine, engineering, and materials science, that has developed to its current form primarily since World War II. Because of the breadth of the field, confusion often exists about what a biomaterial is and, in particular, the role of the biomaterialist in modern medicine. Biomaterials may be defined as nonviable materials used in or as a medical device with the intention of performing a medically related function. Biomaterials have been in existence for a number of years, and their use and number of applications have exploded in the past century.

Gold was one of the first known substances to be used in dentistry. Use of gold dates back about 2000 years. Glass eyes have a shorter history. The use of wooden (George Washington had a set) and, later, ivory dentures dates to the Middle Ages. The advent of aseptic surgery in the 1860s necessarily predated the first successful use of metal bone plates in 1900 and joint replacements in the 1930s. Accidental implantation of plastic shards from shattered airplane turrets during World War II, and the recognition that a major rejection episode did not occur, probably led to the initiation of today's market for biomaterials. Blood vessels were being replaced in the 1950s, heart valves were implanted in the 1960s, and the field has expanded radically since.[1]

Examples of uses of biomaterials include the following:

- Replacement of diseased organs: dialysis with semipermeable membranes (cuprophane, 1960s)
- Treatment aids: catheters
- Replacement of diseased part: dental amalgams
- Replacement of burned or dead part: artificial skin
- Cosmetic correction: breast implants
- Assistive in healing: sutures
- Diagnostic aids: rectoscope
- Functional correction: spinal rods (Harrington)
- Improvement of function: soft contacts
- Monitoring, diagnosis, and treatment: pacemaker with defibrillator

This field is sufficiently broad in scope that there exists, since 1975, the Society for Biomaterials, which coordinates the interests of students, faculty, and industry via an international organization, a searchable website, and national meetings (the website is http://www.biomaterials.org as of this writing). Other websites contain databases for dental materials (University of Michigan; http://www.lib.umich.edu/dentlib/Dental_tables/intro.html) and general materials (MatWeb;

http://www.matweb.com/main.htm). Also of value is the website for the American Society for Artificial Internal Organs (http://www.asaio.com).

Biological evaluation of biomaterial and medical devices using biomaterial is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The device materials should not, either directly or through the release of their material constituents

- Produce adverse local or systemic effects
- Be carcinogenic
- Produce adverse reproductive and developmental effects

Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

When selecting the appropriate tests for biological evaluation of a medical device, one must consider the chemical characteristics of device materials and the nature, degree, frequency, and duration of its exposure to the body. In general, the tests include the following:

- Acutes
- Subchronic and chronic toxicity
- Irritation to skin, eyes, and mucosal surfaces
- Sensitization
- Hemocompatibility
- Genotoxicity
- Carcinogenicity
- Effects on reproduction including developmental effects

However, depending on varying characteristics and intended uses of devices as well as the nature of contact, these general tests may not be sufficient to demonstrate the safety of some specialized devices. Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity, may be necessary for some devices. For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb CSF. The specific clinical application and the materials used in the manufacture of the new device determine which tests are appropriate.

Some devices are made of materials that have been well characterized chemically and physically in the published literature and have a long history of safe use. For the purposes of demonstrating the substantial equivalence of such devices to other marketed products, it may not be necessary to conduct all the tests suggested in the Food and Drug Administration (FDA) matrix of this guidance. FDA reviewers are advised to use their scientific judgment in determining which tests are required for the demonstration of substantial equivalence under section 510(k). In such situations, the manufacturer must document the use of a particular material in a legally marketed predicate device or a legally marketed device with comparable patient exposure.

11.1 THE FDA AND BIOCOMPATIBILITY

In 1986, the FDA, Health and Welfare Canada, and Health and Social Services UK issued the Tripartite Biocompatibility Guidance for Medical Devices. This guidance has been used by FDA

reviewers, as well as by manufacturers of medical devices, in selecting appropriate tests to evaluate the adverse biological responses to medical devices. Since that time, the International Standards Organization (ISO), in an effort to harmonize biocompatibility testing, developed a standard for biological evaluation of medical devices (ISO 10993). The scope of this 12-part standard is to evaluate the effects of medical device materials on the body. The first part of this standard, "Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing," provides guidance for selecting the tests to evaluate the biological response to medical devices. Most of the other parts of the ISO standard deal with appropriate methods to conduct the biological tests suggested in Part 1 of the standard.

The ISO standard, Part 1, uses an approach to test selection that is very similar to the currently used Tripartite Guidance, including the same seven principles. It also uses a tabular format (matrix) for laying out the test requirements based on the various factors discussed previously. The matrix consists of two tables: Initial Evaluation Tests for Consideration (Table 11.1) and Supplementary Evaluation Tests for Consideration (Table 11.2). In addition, the FDA is in the process of preparing toxicology profiles for specific devices. These profiles will assist in determining appropriate toxicology tests for these devices.

To harmonize biological response testing with the requirements of other countries, the FDA will apply the ISO standard, Part 1, in the review process in lieu of the Tripartite Biocompatibility Guidance.

The FDA notes that the ISO standard acknowledges certain kinds of discrepancies. It states, "Due to diversity of medical devices, it is recognized that not all tests identified in a category will be necessary and practical for any given device. It is indispensable for testing that each device shall be considered on its own merits: additional tests not indicated in the table may be necessary." In keeping with this inherent flexibility of the ISO standard, the FDA has made several modifications to the testing required by ISO 10993, Part 1. These modifications are required for the category of surface devices permanently contacting mucosal membranes (e.g., IUDs). The ISO standard would not require acute, subchronic, and chronic toxicity and implantation tests. Also, for externally communicating devices, tissue/bone/dentin with prolonged and permanent contact (e.g., dental cements, filling materials, etc.), the ISO standard does not require irritation and systemic tests. Therefore, the FDA has included these types of tests in the matrix. Although several toxicity, acute, subchronic, and chronic toxicity tests were added to the matrix, reviewers should note that some tests are commonly requested, while other tests are to be considered and only asked for on a case-by-case basis. Thus, the modified matrix is only a framework for the selection of tests and not a checklist of every required test.

Reviewers should avoid proscriptive interpretation of the matrix. If a reviewer is uncertain about the applicability of a specific type of test for a specific device, the reviewer should consult toxicologists in the Office of Device Evaluation (ODE). The FDA expects that manufacturers will consider performing the additional tests for certain categories of devices suggested in the FDA-modified matrix. This does not mean that all the tests suggested in the modified matrix are essential and relevant for all devices. In addition, device manufacturers are advised to consider tests to detect chemical components of device materials, which may be pyrogenic. The FDA believes that ISO 10993, Part 1, and appropriate consideration of the additional tests suggested by knowledgeable individuals will generate adequate biological data to meet its requirements.

Manufacturers are advised to initiate discussions with the appropriate review division in the ODE, Center for Devices and Radiological Health (CDRH), prior to the initiation of expensive, long-term testing of any new device materials to ensure that the proper testing will be conducted. We also recognize that an ISO standard is a document that undergoes periodic review and is subject to revision. The ODE will notify manufacturers of any future revisions to the ISO standard referenced here that affect this document's requirements and expectations.

TABLE 11.1
Initial Evaluation Tests for Consideration

Device Categories			Biological Effect							
Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation	System Toxicity	Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility
Surface devices	Skin	A	X	X	X	.	.	.	.	.
		B	X	X	X	.	.	.	.	.
		C	X	X	X	.	.	.	.	.
	Mucosal membrane	A	X	X	X	.	.	.	.	.
		B	X	X	X	O	O	.	O	.
		C	X	X	X	O	X	X	O	.
	Breached or compromised surfaces	A	X	X	X	O	.	.	.	.
		B	X	X	X	O	O	.	O	.
		C	X	X	X	O	X	X	O	.
External communicating devices	Blood path, indirect	A	X	X	X	X	.	.	.	X
		B	X	X	X	X	O	.	.	X
		C	X	X	O	X	X	X	O	X
	Tissue/bone/ dentin communicating	A	X	X	X	O	.	.	.	.
		B	X	X	O	O	O	X	X	.
		C	X	X	O	O	O	X	X	.
	Circulating blood	A	X	X	X	X	.	O	.	X
		B	X	X	X	X	O	X	O	X
		C	X	X	X	X	X	X	O	X
Implant devices	Tissue/bone	A	X	X	X	X	O	.	.	.
		B	X	X	O	O	O	X	X	.
		C	X	X	O	O	O	X	X	.
	Blood	A	X	X	X	X	.	.	X	X
		B	X	X	X	X	O	X	X	X
		C	X	X	X	X	X	X	X	X

Note: A, 24 h; B, 24 h–30 days; C, >30 days; O, additional tests that may be applicable; X, ISO evaluation tests for consideration.

TABLE 11.2
Supplementary Evaluation Tests for Consideration

Device Categories			Biological Effects			
Body Contact		Contact Duration	Chronic Toxicity	Carcinogenicity	Reproductive Development	Biodegradable
Surface devices	Skin	A	.	.	.	.
		B	.	.	.	.
		C	.	.	.	.
	Mucosal membrane	A	.	.	.	.
		B	.	.	.	.
		C	O	.	.	.
	Breached or compromised surfaces	A	.	.	.	.
		B	.	.	.	.
		C	O	.	.	.
External communicating devices	Blood path, indirect	A	.	.	.	.
		B	.	.	.	.
		C	X	X	.	.
	Tissue/bone/dentin communicating	A	.	.	.	.
		B	.	.	.	.
		C	O	X	.	.
	Circulating blood	A	.	.	.	.
		B	.	.	.	.
		C	X	X	.	.
Implant devices	Tissue/bone	A	.	.	.	.
		B	.	.	.	.
		C	X	X	.	.
	Blood	A	.	.	.	.
		B	.	.	.	.
		C	X	X	.	.

Note: A, 24 h; B, 24 h–30 days; C, >30 days; O, additional tests that may be applicable; X, ISO evaluation tests for consideration.

11.2 INTERNATIONAL REGULATORY EFFORTS

The ISO is in the process of publishing a series of standards on the biological evaluation of medical devices—ISO 10993. Many parts of this series have been accepted as international standards, while the rest are under development (see Table 11.3). The subject of the first part, ISO 10993-1, is the categorizing and performance of safety testing. Part two of the standard, ISO 10993-2, is concerned with animal welfare requirements; another section, ISO 10993-12, deals with sample preparation and reference materials. Most of the remaining parts of the standard treat the individual tests.

The European Union (EU) has issued a council directive—93/42/EEC, 1993—concerning medical devices. All medical devices to be sold on the EU market must comply with this directive after June 14, 1998. The European Committee for Standardization (CEN) is currently in the process of adopting the ISO 10993 standard as the European standard. In 1986, the responsible authorities in the United Kingdom, the United States, and Canada issued the Tripartite document, which was guidance on the selection of toxicological tests for medical device safety testing. This document has now been replaced by ISO 10993-1 as a first step in the process of international harmonization. In

TABLE 11.3
Individual Parts of ISO 10993

Part	Title
1	Evaluation and Testing
2	Animal Welfare Requirements
3	Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity
4	Selection of Tests for Interactions with Blood
5	Tests for Cytotoxicity—In Vitro Methods
6	Tests for Local Effects after Implantation
7	Ethylene Oxide Sterilization Residuals
8	Clinical Investigation of Medical Devices
9	Degradation of Materials Related to Biological Testing
10	Test for Irritation and Sensitization
11	Test for Systemic Toxicity
12	Sample Preparation and Reference Material
13	Identification and Quantification of Degradation Products from Polymers
14	Identification and Quantification of Degradation Products from Ceramics
15	Identification and Quantification of Degradation Products from Coated and Uncoated Metals and Alloys
16	Toxicokinetic Study Design for Degradation Products and Leachables
17	Glutaraldehyde and Formaldehyde Residues in Industrially Sterilized Medical Devices

1995 the FDA chose to accept the ISO 10993-1 standard, with a modification of the matrix listing (see sidebar). Japanese authorities have also issued a guideline for toxicological testing of medical devices. This document is available in an unofficial translation as Guidelines for Basic Biological Tests of Medical Materials and Devices. It resembles ISO 10993 in structure and content but recommends modified tests and sample preparations.

The procedure for using the ISO 10993-1 standard is illustrated by the flowchart in Figure 11.1. The standard is applicable only for devices that are directly or indirectly in contact with the body or body fluids. If a device is to be subjected to the standard, the first step is to characterize the material. Such characterization need not always be followed by biological evaluation, because there may be sufficient historical data to verify that the device meets the requirements of the standard. If the material and/or the intended use of the device is different from any historical safe device, biological evaluation has to be performed. By following the standard, a suitable test program can be chosen depending on the type and duration of body contact. Within the EU, all new medical devices must carry the CE (European Certification) mark from June 14, 1998. This should ensure the availability of relevant documentation regarding biocompatibility and the lack of health problems associated with the use of a device. It is noteworthy that the approval of such documentation is accorded not, as it was previously, by the national health authorities but, rather, by the so-called notified bodies, whose experts review the products and production facilities of medical device manufacturers.

11.3 DEVICE CATEGORY AND CHOICE OF TEST PROGRAM

The need to evaluate a medical device biologically depends on the material used in the device, the intended body contact, and the duration of that contact. A device designed for surface contact for a limited time is not as likely to be bioincompatible as a permanent-exposure implant device made of the same material. The ISO 10993-1 standard divides medical devices into three main categories: surface devices, externally communicating devices, and implant devices. Each category is further

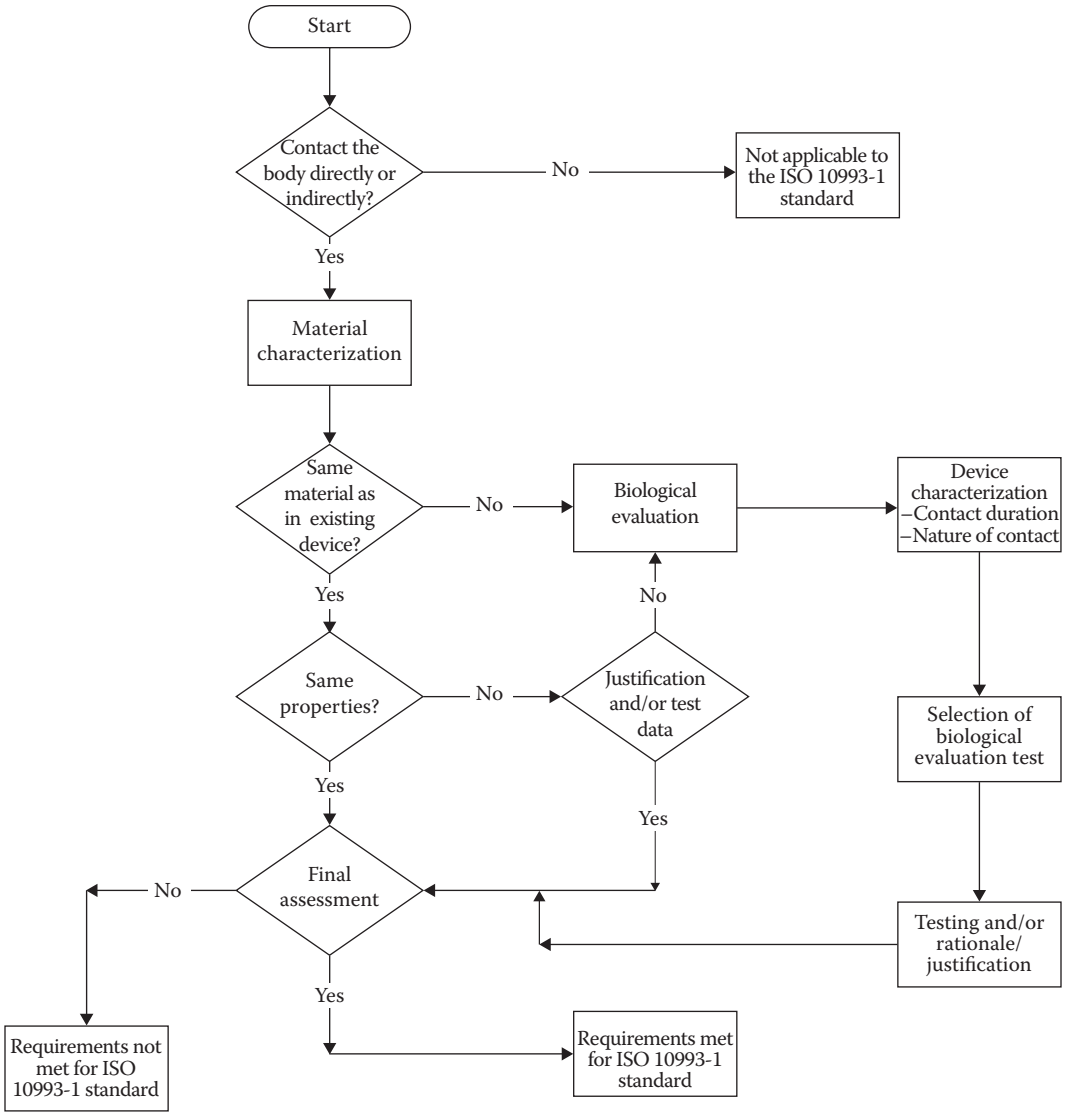

FIGURE 11.1 Steps in the biological evaluation of medical devices.

divided into subcategories according to the type of contact to which the patient is exposed (see Table 11.4).

The ISO test matrix should be considered not as a checklist for the different tests that have to be performed but, rather, as a guide for qualified toxicologists who also take into consideration material information and historical data from similar devices. The certifying authorities in most countries (e.g., notified bodies, FDA, Japanese authorities) are generally cooperative when a company must decide on a test program for a device. It is therefore advisable to maintain close contact with the relevant authorities during the entire process. However, testing should not be performed simply to meet regulatory requirements. This is important not only to lessen the risk of overtesting and excessive use of experimental animals but also because a strict regulatory approach may mask potential negative health effects that might be identified via optional or nonroutine testing procedures.

TABLE 11.4
Device Categories and Examples according to ISO 10993-1

Device Categories		Examples
Surface devices	Skin	Electrodes, external prostheses, fixation tapes, compression bandages, monitors (various types)
	Mucous membrane	Contact lenses, urinary catheters, intravaginal and intraintestinal devices, endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices
	Breached or compromised surfaces	Ulcer, burn, and granulation tissue dressings or healing devices; occlusive patches
Externally communicating devices	Blood path indirect	Solution administration sets, extension sets, transfer sets, blood administration sets
	Tissue/bone/dentin communicating	Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials, skin staples
	Circulating blood	Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, hemoadsorbents and immunoadsorbents
Implant devices	Tissue/bone	Orthopedic pins, plates, replacement joints, bone prostheses, cements and intraosseous devices, pacemakers, drug-supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips
	Blood	Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters, ventricular-assist devices

The choice of test program for a device in a given category depends on the duration of the contact. Three different time spans are given: limited contact (<24 hours), prolonged contact (24 hours–30 days), and permanent contact (>30 days). ISO 10993-1 lists the tests that must be considered for each category.

As regards CE marking of existing products on the market or safety evaluation of medical devices already in clinical use, appropriate historical or clinical data should be employed whenever possible to avoid unnecessary testing.

11.4 PREPARATION OF EXTRACTS

ISO 10993-12 describes how samples for biological evaluation should be selected, prepared, and extracted. Other guidelines provide similar descriptions, which differ slightly in the specifics of the extraction procedures.

The device to be tested (the test article) should be a representative specimen of the mass-produced device. It should also be finished or treated (e.g., coated or sterilized) in the same way as the mass-produced device.

Because the toxic potential of materials and devices depends to a substantial degree on the leachability and toxicity of soluble components, extracts of the device are normally used in the tests. In some tests, however, an evaluation under normal-use conditions is mimicked by using the device or a piece of the device directly. Ideally, extraction media should constitute a series of media with decreasing polarity to ensure the extraction of components of widely different solubility properties. The most commonly used extraction media are physiological saline, vegetable oil, dimethyl sulfoxide, and ethanol. Other extraction media such as polyethylene glycol or aqueous dilutions of ethanol may be selected in certain cases. For in vitro cytotoxicity testing, complete cell-culture medium is most often employed. The various guidelines also differ somewhat with respect to the temperature

at which the extraction is conducted. Some leachable compounds may be chemically altered at high temperatures, and it is now generally recommended that extraction be conducted at 37°C—simulating body temperature—for 72 hours. This procedure will probably become increasingly accepted as the most appropriate extraction method. For in vitro cytotoxicity tests, extraction at 37°C for 24 hours is usually recommended, since certain constituents of the media are relatively labile.

The amount of leachable substances released to the extraction media is related to the surface area and thickness of the product to be extracted. Recommendations vary from 1.25 to 6 cm^2 of product per milliliter of extraction medium, depending on the size and shape of the product, or from 0.1 to 0.2 g of product per milliliter of extraction medium when a surface area cannot readily be estimated (e.g., for powders or granulates). In any case, the specific properties of the product must be taken into account in order to make usable extracts.

For cases in which a medical device comprises several components made from different materials, the ideal procedure from a toxicological point of view would be to test extracts of the components separately. However, in some situations, this is not practical, and extracts of the whole device may be used instead.

11.5 BIOLOGICAL CONTROL TESTS

Biological control tests are not described in the ISO 10993 standard for biological evaluation of medical devices, since these particular tests are designed primarily for batch-control purposes. Such tests are also used during the product development phase to identify sources of contamination and to establish procedures that ensure the intended quality of the end product.

11.5.1 Microbiological Control Tests

Microbiological control tests are necessary to establish the microbiological status of an end product—factors such as sterility, absence of pathological bacteria, or limits for microbial counts. Furthermore, it is often necessary to monitor the microbiological load of raw materials and intermediary products or to check the efficiency of production and sterilization processes. The tests are performed by rinsing the materials or products in physiological saline and assessing the rinsing medium for microbes, or by directly incubating the products in growth media.

11.5.2 Tests for Endotoxins

Even sterile medical devices may contain cell-wall lipopolysaccharides originating from gram-negative bacteria. Such so-called endotoxins or pyrogens can cause an abrupt fever reaction after entering directly into the body from sources such as venous catheters, syringes, or implant components. Two different biological assays can be used to measure the presence of endotoxins: the rabbit pyrogen test and the Limulus test. In both cases, an eluate is prepared—normally by rinsing the surfaces of the product with water—and then tested for endotoxins. In the rabbit pyrogen test, the eluate is injected intravenously, and the rectal temperature of the animal is measured after the injection. In the Limulus test, the eluate is incubated together with lysate from the blood of the horseshoe crab (*Limulus polyphemus*), which contains a substance that forms a gel in the presence of endotoxins.

11.5.3 Test for Nonspecific Toxicity

This test is designed to assess any nonspecific adverse effect that occurs following intravenous injection of a device eluate in mice. The test is often performed with the same eluate used for the pyrogen test. The mice are inspected regularly for any signs of ill health, which can indicate the presence of toxic substances leaching from the product.

11.6 TESTS FOR BIOLOGICAL EVALUATION

This section provides a brief description of the individual tests included in the ISO 10993/EN 30993 standard.

11.6.1 Cytotoxicity

The aim of in vitro cytotoxicity tests is to detect the potential ability of a device to induce sublethal or lethal effects as observed at the cellular level. According to ISO 10993-1, the in vitro cytotoxicity assay is one of two tests—the other is the sensitization test described later—that must be considered in the evaluation of all device categories.

Three main types of cell-culture assays have been developed:

- Elution test
- Direct-contact test
- Agar diffusion test

In the elution test, an extract (eluate) of the material is prepared and added in varied concentrations to the cell cultures. Growth inhibition is a widely used parameter, but others may also be used. In the direct-contact test, pieces of test material are placed directly on top of the cell layer, which is covered only by a layer of liquid cell-culture medium. Toxic substances leaching from the test material may depress the growth rate of the cells or damage them in various ways. In the agar diffusion test, a piece of test material is placed on an agar layer covering a confluent monolayer of cells. Toxic substances leaching from the material diffuse through the thin agar layer and kill or disrupt adjacent cells in the monolayer. As always, the physical and chemical properties of the test material should be considered before the choice of the test system is made.

There is usually a good qualitative correlation between results from cell-culture tests and studies performed in vivo with respect to cytotoxicity versus primary tissue effects. It is important to recognize, however, that although cell-culture toxicity is, in general, a good and sensitive indicator of primary tissue compatibility, exceptions may arise in cases where leaching substances cause tissue damage in vivo through more complex mechanisms. At present, the in vitro cytotoxicity assays should be used as screening tests and considered primarily as supplements to the various in vivo tests.

11.6.2 Sensitization

The sensitization test recognizes a potential sensitization reaction induced by a device and is required by the ISO 10993-1 standard for all device categories. The sensitization reaction is also known as allergic contact dermatitis, which is an immunologically mediated cutaneous reaction. This is in contrast to irritant contact dermatitis (skin irritation)—a skin reaction caused by the primary and direct effect of a substance on the skin. In animals, the sensitization reactions manifest themselves as redness (erythema) and swelling (edema).

The preferred animal species for sensitization testing is the albino guinea pig. There is no reliable alternative in vitro test that can predict the sensitizing potential of a substance. The various available guinea pig methods have certain features in common: an induction (sensitization) phase, when the potential allergen is presented to the organism, followed by a rest period and a subsequent challenge phase to determine whether or not sensitization has occurred.

One of the most recognized and validated assays is the guinea pig maximization test (GPMT). A test design very similar to the GPMT is widely used for assessing the sensitizing potential of medical

devices. After a challenge period, the skin reactions are graded on a ranking scale according to the degree of erythema and edema.

Predictive tests in guinea pigs are important tools in identifying the possible hazard to a population repeatedly exposed to a substance. Nevertheless, results from sensitization tests in guinea pigs have to be evaluated carefully. A positive test result in this assay may result in the rating of a substance as a stronger sensitizer than it appears to be during actual use. On the other hand, a negative result in such a sensitive assay ensures a considerable safety margin regarding the potential risk to humans.

11.6.3 Skin Irritation

The ISO 10993-10 standard describes skin-irritation tests for both single and cumulative exposure to a device. The preferred animal species is the albino rabbit, whose highly sensitive, light skin makes it possible to detect even very slight skin irritation caused by a substance. Skin-irritation tests of medical devices are performed either with two extracts obtained with polar and nonpolar solvents or with the device itself.

In the single-exposure test, rabbits are treated for several hours only, whereas for the cumulative test, the same procedure is repeated for several days. All extracts and extractants are applied to intact skin sites. Skin reaction is seen as redness or swelling and is graded according to a specified classification system. Dermal irritation is the production of reversible changes in the skin following the application of a substance, whereas dermal corrosion is the production of irreversible tissue damage (scar formation) in the skin. Materials that leak corrosive substances are not likely candidates for medical device production.

11.6.4 Intracutaneous Reactivity

The intracutaneous reactivity test is designed to assess the localized reaction of tissue to leachable substances. The test is required for consideration in nearly all the device categories in ISO 10993-1 (see Table 11.3). Polar and nonpolar solvent extracts are administered as intracutaneous injections to rabbits. Undesirable intracutaneous reactivity includes redness or swelling.

11.6.5 Acute Systemic Toxicity

Acute systemic toxicity is the adverse effect occurring within a short time after administration of a single dose of a substance. ISO 10993-1 requires that the test for acute systemic toxicity be considered for all device categories that indicate blood contact. For this test, extracts of medical devices are usually administered intravenously or intraperitoneally in rabbits or mice.

Determining acute systemic toxicity is usually an initial step in the assessment and evaluation of the toxic characteristics of a substance. By providing information on health hazards likely to arise from short-term exposure, the acute systemic toxicity test can serve as a first step in the establishment of a dosage regimen in subchronic and other studies and can also supply initial data on the mode of toxic action of a substance. The test is similar to the nonspecific toxicity test. Normally, only one of these two procedures is included in a test battery.

11.6.6 Genotoxicity

Genetic toxicology tests are used to investigate materials for possible mutagenic effects—that is, damage to the body's genes or chromosomes. The tests are performed both in vitro and in vivo. ISO 10993-1 requires the genotoxicity (mutagenicity) test to be considered for all device categories indicating permanent (>30 days) body contact (except for surface devices with skin contact only).

A mutation is a change in the formation content of the genetic material (DNA code) that is propagated through subsequent generations of cells. Mutations can be classified into two general types:

- Gene mutations
- Chromosomal mutations

Gene mutations are changes in nucleotide sequences at one or several coding segments within a gene; chromosomal mutations are morphological alterations or aberrations in the gross structure of the chromosomes.

The simplest and most sensitive assays for detecting induced gene mutations are those using bacteria. Gene mutations can also be detected in cultured mammalian cells. Current in vivo assays for gene mutations are cumbersome and not widely used. The simplest and most sensitive assays for investigating chromosomal aberrations are those that use cultured mammalian cells. However, two well-established in vivo procedures are also available: chromosomal aberrations can be studied in bone marrow or peripheral blood cells of rodents dosed with a suspect chemical or extract either by counting micronuclei in maturing erythrocytes (micronucleus test) or by analyzing chromosomes in metaphase cells.

In addition to these mutagenicity tests, various assays can measure the induction of an overall genotoxic response—an indirect indicator of potential damage to the genetic material.

11.6.7 Implantation

Implantation tests are designed to assess any localized effects of a device designed to be used inside the human body. Implantation testing methods essentially attempt to imitate the intended use conditions of an implanted material. Although different tests use various animal species, the rabbit has become the species of choice, with implantation performed in the paravertebral muscle. Implantation can be either surgical or nonsurgical: the surgical method involves the creation of a pouch in the muscle into which the implant is placed, while the nonsurgical method uses a cannula and stylet to insert a cylinder-shaped implant. Through a macroscopic examination (which may be supplemented with microscopic analysis), the degree of tissue reaction in the paravertebral muscle is evaluated as a measure of biocompatibility.

11.6.8 Hemocompatibility

The purpose of hemocompatibility testing is to look for possible undesirable changes in the blood caused directly by a medical device or by chemicals leaching from a device. Undesirable effects of device materials on the blood may include hemolysis, thrombus formation, alterations in coagulation parameters, and immunological changes. According to the ISO 10993-4 (EN 30993-4) standard, devices that only come into very brief contact with circulating blood—for example, lancets, hypodermic needles, or capillary tubes—generally do not require blood/device interaction testing.

ISO 10993-4 describes hemocompatibility tests in five different categories:

- Thrombosis
- Coagulation
- Platelets
- Hematology
- Immunology

Most of the individual tests are not discussed in detail, but they may be performed either in vivo or, preferably, in vitro. There is still some uncertainty with respect to what is actually required by the regulatory authorities for the hemocompatibility test.

11.6.9 Subchronic and Chronic Toxicity

Subchronic toxicity is the potentially adverse effect that can occur as a result of the repeated daily dosing of a substance to experimental animals over a portion of their life span. In the assessment and evaluation of the toxic characteristics of a chemical, the determination of subchronic toxicity is carried out after initial information on toxicity has been obtained by acute testing and provides data on possible health hazards likely to arise from repeated exposures over a limited time. Such testing can furnish information on target organs and the possibilities of toxin accumulation and can provide an estimate of a no-effect exposure level that can be used to select dose levels for chronic studies and establish safety criteria for human exposure.

In subchronic or chronic toxicity studies, one or two animal species are dosed daily, usually for a period of 3 to 6 months; the rat is the standard animal species of choice. The animals are given the test substance in increasing doses. The dose level of the low-dose group should be at the level of human exposure. When extracts of medical devices are employed, one dose level (the highest practically applicable volume) is often sufficient, since strong toxicity is generally not expected.

11.6.10 Carcinogenicity

The objective of long-term carcinogenicity studies is to observe test animals over a major portion of their life span to detect any development of neoplastic lesions (tumor induction) during or after exposure to various doses of a test substance. Carcinogenicity testing is normally conducted with oral dosing. For implants and medical devices, however, only extracts can be tested, and they must be administered intravenously, necessitating certain modifications of the standard procedure. There are only a very few products for which this comprehensive test can be justified.

In carcinogenicity studies, mice or rats are dosed every day for 18 to 24 months. For medical device extracts, one dose level (again, the highest practically applicable volume) is usually sufficient. At the completion of the dosing period, all surviving animals are sacrificed, and their organs and tissues are examined microscopically for the presence of tumors. An increased incidence of one or more category of tumors in the dosed group would indicate that the product tested has the potential to induce tumors and could be considered a possible carcinogen in humans.

11.7 ALTERNATIVE TEST METHODS

As mentioned previously, a major goal in international toxicological testing is to reduce not only the use of in vivo studies but also the number of animals employed in these tests. A few of the in vivo procedures used today for testing medical devices may be of questionable worth for safety evaluation. However, the availability of accepted and validated in vitro assays is still limited. Substantial resources have been made available for validation of alternative in vitro assays in toxicology as replacements for animal tests, but it may take years before validated methods can be implemented, and any goal of replacing all in vivo studies with in vitro assays will probably never be met.

Recently, a working group under the auspices of the European Center for Validation of Alternative Methods (ECVAM) has recommended a few alternative methods that can be used for safer testing of medical devices. These include two in vitro tests as potential substitutes for the in vivo assays for skin and eye irritation. However, the implementation of validated protocols and internationally accepted guidelines for these tests is likely to be delayed into the next century.

11.8 OTHER CONSIDERATIONS FOR DESIGN

The reader of this text is assumed to have had some exposure to materials science via coursework or otherwise. Many databases exist that can aid in the development of nonbiological contacting

materials; one highly recommended source is http://www.matweb.com. For design processes that might involve medical devices, a software package from http://www.grantadesign.com includes access to a database for materials involved in medical devices. Educational pricing is available with this package, which has been used in biomaterials courses at several institutions.

11.9 MATERIALS DESIGN EXAMPLE

In the early 1990s, author King was contacted by a manufacturer of a safety garment that was designed to protect physicians and others working in close contact with AIDS patients (for surgical and other procedures involving possible contact with body fluids). The outfit consisted of a gown and shoe cover system that was water-impermeable, similar to a complete coverall raincoat system. A translucent pane of cellophane-like material allowed for visual access to the patient. A flap at the bottom of this "windowpane" allowed for minor (but sufficient) air access. Regulation latex or other gloves completed the almost compote isolation of the health care worker from the environment.

The manufacturer stated that the garment system was not selling and offered to bring several of the outfits to be tested by King. (Implicit in this discussion was that King was to be used as a consultant, but no contract was signed.) Several of the outfits were brought to King's office; introductory comments were made that the outfits were uncomfortable in use.

King tried on one of the outfits and, within a few minutes, was extremely hot and sweaty. There was no means of ventilation other than the minor amount of air being exchanged with breathing. As a result, the expired air at 100% humidity and ~98.6°F temperature quickly drove the inner environ of the outfit to uncomfortable temperatures.

With his background in anesthesiology, two solutions were immediately obvious to King, and he mentioned them. An already extent solution for similar gowns was to pressurize them with the reverse flow from a vacuum cleaner. This would allow for cool air to enter the gown and would assist in, due to the pressure gradient, further isolating the worker from possible contamination. (Mobility is impaired, however.) A second solution based upon prior experiences was a materials science solution. The author knew that when patient expired air is suctioned for injection to a capnometer for CO_2 measurement, the tubing is typically Nafion plastic tubing, which allows the humid air to equilibrate with room air extremely quickly (to not affect the CO_2 measurement). This solution was also suggested as the faceplate material, and a skullcap section could easily be replaced by Nafion plastic.

The author was thanked; payment became several of the outfits, which were later used in the design class as a "put-yourself-in-the-picture" example.

11.10 ENDNOTE

There have been some disasters involving biomaterials. These disasters have emphasized the need for diligence in testing of biomaterials. These include toxic shock syndrome, latex allergies, the use of talc on gloves, and perhaps reactions to silicon gel leakage from breast implants. Continuing diligence, especially when new substances are being tested, is mandated by law.

EXERCISES

1. You are charged with developing the coating material for an implantable brain stimulator for reduction of tremor due to Parkinson's disease. You may begin with a web search to determine what materials are currently in use, if any. What materials will you consider, and what tests will need to be run? Refer to the charts in this chapter.
2. You are interested in building an inexpensive electrocardiogram (EKG) transmitter for implantation in mice. Do a literature (or web) search to determine a list of acceptable coatings. Which would you use if the experiment were to only last 1 day? Which if the work was to continue for a month? Why?

3. Do a literature search to determine the history of implant materials. What are some of the earliest signs that the human body accepted a foreign object?
4. How old is the history of implantation of materials into human teeth? Why was this done?
5. Do a web search using the term "biocompatibility testing"; categorize the first several hits as to their relevance to this chapter. Do a similar search using the term "animal care and use form."
6. Why are rabbits so often used for pyrogen testing? What is unique about rabbits?
7. The horseshoe crab is of value in compatibility testing. What is special about this animal?
8. "The use of earrings and other body piercing adornments has been linked to an increase in one of the hepatitis strains in the users." Do a web or literature search to deny or defend this statement.
9. In post-war Germany, an operation called a cineplasty was performed on amputees, wherein a carbon-coated rod was passed through the muscle above the amputation. With time, the tunnel often grew skin on its surface, and the subject could use his/her remaining muscle to move prostheses, such as a primitive grasper hand. Research this history and speculate on what might ensue if there had been no long-term problems.
10. Research one of the four problems referenced in the endnote section. What was involved in the problem, and what was the outcome?

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12 Risk Analysis
Devices and Processes

Early and provident fear is the mother of safety.

Edmund Burke

Risk analysis for readers of this text may imply analysis of potential harm caused by devices and harm caused by processes. This chapter will consider risk analysis first as concerned (primarily) with devices (Sections 12.1 to 12.7) and then with processes (remainder).

Medical devices have become a visible and dramatic part of modern medical care. The period following World War II has seen the development of a tremendous range of devices that have revolutionized medical practice and improved or prolonged millions of lives. At the same time, devices are not automatically beneficial, and they, like all technology, are associated with risk. Recent examples include ultrasound equipment that often does not comply with electrical safety guidelines, leakage of insulin pumps, defective artificial cardiac valves, and reactions of the body to materials used in implants.

Issues of balancing risk and benefit are familiar in the field of drugs. Drugs are regulated for efficacy and safety in most countries, and many countries make concerted attempts to influence how drugs are prescribed. International organizations, such as Health Action International, continually monitor safety and efficacy with regard to drugs. Devices, however, get much less attention. It seems they are almost ignored despite their similarities to drugs. They are as follows:

- Pervasive in medical care
- Products made and marketed by a profit-making industry
- Often taken into the body
- Associated with demonstrable problems of efficacy and safety

In addition, they are linked to important economic effects in terms of health care expenditures and the strength of national industrial efforts.

12.1 SAFETY

Safety may be defined as freedom from accidents or losses. Some people have argued that there is no such thing as absolute safety, and therefore, safety should be defined in terms of acceptable losses. Using this argument, an alternative definition of safety would be a judgment of the acceptability of risk, with risk, in turn, as a measure of probability and severity of harm to human health.

A product is safe if its attendant risks are judged to be acceptable. This definition of safety implies that hazards cannot be eliminated, when they often can. While in most instances, all hazards cannot be eliminated, specific hazards can be totally eliminated from a product or system.

System safety is a subdiscipline of systems engineering that applies scientific, management, and engineering principles to ensure adequate safety throughout the system life cycle, without constraints of operational effectiveness, time, and cost. Although safety has been defined as freedom

from those conditions that can cause death, injury, occupational illness, or damage to or loss of equipment or property, it is generally recognized that this is unrealistic. By this definition, any system that presents an element of risk is unsafe. But almost any system that produces personal, social, or industrial benefits contains an indispensable element of risk.

The problem is complicated by the fact that attempts to eliminate risk often result in risk displacement rather than risk elimination. Benefits and risks often have trade-offs, such as trading off the benefits of improved medical diagnosis capabilities against the risks of exposure to diagnostic x-rays. Unfortunately, the question "How safe is safe enough?" has no simple answer.

Safety is also relative in that nothing is completely safe under all conditions. There is always some case in which a relatively safe material or piece of equipment becomes hazardous. The act of drinking water, if done to excess, can cause kidney failure. Thus, safety is a function of the situation in which it is measured. One definition might be that safety is a measure of the degree of freedom from risk in any environment. To understand safety better, it is helpful to consider the nature of accidents in general.

An accident is traditionally defined by safety engineers as an unwanted and unexpected release of energy. However, release of energy is not involved in some hazards associated with new technologies and potentially lethal chemicals. Therefore, the term *mishap* is often used to denote an unplanned event or series of events that result in death, injury, occupational illness, damage to or loss of equipment or property, or environmental harm. The term *mishap* includes both accidents and harmful exposures.

Mishaps are almost always caused by multiple factors, and the relative contribution of each factor is usually not clear. A mishap can be thought of as a set of events combining in random fashion or, alternatively, as a dynamic mechanism that begins with the activation of a hazard and flows through the system as a series of sequential and concurrent events in a logical sequence until the system is out of control and a loss is produced. The high frequency of complex, multifactorial mishaps may arise from the fact that the simpler potential mishaps have been anticipated and handled. However, the very complexity of the events leading up to a mishap implies that there may be many opportunities to interrupt the sequences.

Mishaps often involve problems in subsystem interfaces. It appears to be easier to deal with failures of components than failures in the interfaces between components.

How do engineers deal with safety problems? The earliest approach to safety, called operational or industrial safety, involves examining the system during its operational life and correcting what are deemed to be unacceptable hazards. In this approach, accidents are examined, causes are determined, and corrective and preventive actions are initiated. In some complex systems, however, a single accident can involve such a great loss as to be unacceptable. The goal of risk analysis is to design an acceptable safety level into the system before actual production or operation.

Risk analysis attempts to optimize safety by applying scientific and engineering principles to identify and control hazards through analysis, design, and management processes.

12.2 RISK

The term *risk* is defined as the probable rate of occurrence of a hazard causing harm and the degree of severity of the harm. The concept has two elements:

- The possibility of a hazardous event
- The severity of the consequences of that hazardous event

The probability of occurrence may be classified into various levels as described in Table 12.1. The levels of severity may be classified as indicated in Table 12.2. The U.S. Food and Drug Administration

TABLE 12.1
Probability of Occurrence Table

Probability of Occurrence	Consequence
Frequent	Likely to occur often
Probable	Will occur several times in the lifetime of the device
Occasional	Likely to occur sometime in the lifetime of the device
Remote	Unlikely to occur but possible
Improbable	Probability of occurrence indistinguishable from zero
Impossible	Probability of occurrence is zero

TABLE 12.2
Hazard Severity Table

Severity Level	Consequence
Catastrophic	Potential of resulting in multiple deaths or serious injuries
Critical	Potential of resulting in death or serious injury
Marginal	Potential of resulting in injury
Negligible	Little or no potential to result in injury

(FDA) has rated medical devices into three levels of concern, major, moderate, and minor. The severity levels in Table 12.2 approximate the FDA levels as follows:

- Major Critical
- Moderate Marginal
- Minor Negligible

Risk may be graphed into three regions when analyzing the probabilities of occurrence and the levels of severity (Figure 12.1). The risk regions are classified as follows:

- The intolerable region
- The as-low-as-reasonably-practical region
- The broadly acceptable region

The intolerable region contains the risk of some hazards that are so severe that a system that incorporated them would not be tolerated. A risk in this region has to be reduced by reducing either the severity and/or the probability of occurrence.

The region between the intolerable and the broadly acceptable is called the as-low-as-reasonably-practical (ALARP) region. In this region, risks are reduced to the lowest practical level, bearing in mind the benefits of accepting the risk and the cost of further risk reduction. Any risk must be reduced to a level that is ALARP. Near the limit of intolerable risk, risks would normally be reduced, even at considerable cost. Risks near the broadly acceptable region would be reduced if reasonable to do so, but the measure of reasonableness will have been raised. If the risk occurs between the intolerable and broadly acceptable and if the ALARP principle has been applied, the resulting risk is the acceptable risk for that particular hazard.

In some cases, either the severity and/or the probability of occurrence is so low that the risk is negligible compared with the risk of other hazards that are accepted. Risk reduction, in this broadly acceptable region, need not be actively pursued.

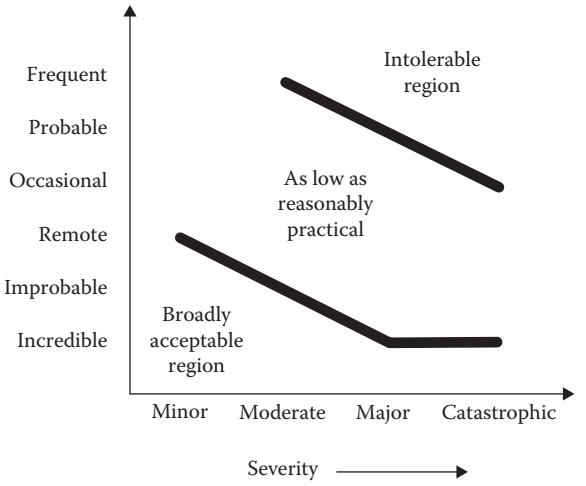

FIGURE 12.1 Risk probability regions.

12.3 DECIDING ON ACCEPTABLE RISK

There is no standard that defines acceptable risk. It is planned that particular device standards will give guidance. Often, acceptable risk has to be established on a case-by-case basis, based on the intended application and the operating environment. Some guidance may be obtained by interpreting the single fault condition and from the performance of similar equipment already in use.

In the case of medical equipment, it may be that the risk associated with the equipment would be acceptable if the prognosis were improved. This cannot be used as an excuse for unnecessary risk.

12.4 FACTORS IMPORTANT TO MEDICAL DEVICE RISK ASSESSMENT

The FDA's experience with medical devices suggests that the factors that are important to medical device risk assessment relate to the device itself and to how it is used. Table 12.3 shows those categories and the major elements of each.

12.4.1 Device Design and Manufacture

A device can present a hazard if it is poorly manufactured or if insufficient attention is paid to design elements that influence performance. For example, the failure to design a structural component to resist the stress to which it will be subjected could lead to its fracture. Quality control or quality assurance during manufacturing may not correct the problem. The FDA's experience suggests

TABLE 12.3
Important Risk Factors

For the Device	For Device Use
Design	Adequacy of instructions
Human factors engineering	Training of users
Manufacturing of quality control and quality assurance	Interaction with other devices
Material's toxicity	Human factors engineering
Material's degradation	

strongly that good manufacturing practices do not eliminate inherently bad designs and could simply ensure that a bad design is faithfully produced. Alternatively, inattention to manufacturing quality assurance could unintentionally cause a device defect.

Device hazards also can be considered in terms of whether the product does something that can cause harm, or whether the product fails to provide a benefit that it is intended to have. For example, patients and health professionals may be harmed by an electric shock from a supposedly insulated device. A missed diagnosis, on the other hand, caused by a malfunction of a device, could lead to inappropriate therapy or no therapy at all, each with dire consequences for the patient. It is important to the eventual management of risk to determine if the hazard arises from omission or commission.

12.4.2 Materials

Materials from which devices are made are a part of the design and manufacturing process considerations. Proper design includes selection of appropriate materials. Good manufacturing practice includes process validation to ensure that the material's properties are not compromised. It is also important to consider materials separately when the device in question is applied to or implanted in the body. In this regard, both the effect of the material on the body and the effect of the body on the material are important.

12.4.3 Device Users

The FDA's experience has repeatedly and consistently shown that the way a device is used is a significant part of the overall safety and effectiveness of that device. From the sample collection procedures that can influence the result obtained from an in vitro diagnostic device to the poor x-ray film processing techniques that lead to the need for a retake, experience clearly indicates the importance of the user.

The user of a medical device can be a health care professional, a patient, or a family member. There is a large variability in users' skills, due to factors such as education and training, health status, environment, and motivation. Whatever the capability of a particular user, circumstances occur that can be a controlling influence, such as the inattention that can result when a tired individual tries to perform a repetitive task.

The user also represents the decision point on the application of medical technology. The decision may be wrong. Patients may inappropriately rely on over-the-counter devices.

The kinds of hazards that may result from user error are not unusual in themselves. What is unusual is that the incidence of such hazards occurring can range from nonexistent to frequent depending on the influence of the user. Thus, the training of the user and the adequacy of the instructions provided with the device relate directly to assessing the aforementioned risks.

12.4.4 Human Factors

Human factors are those device design elements and use conditions that influence how the device and the user interact. This interaction places an additional complexity on the ability to identify the hazards that might be associated with a particular device. Without considering human factors as part of the risk assessment, it would have been difficult to consider the appropriate risk management approach.

12.4.5 Medical Device Systems

The device-intensive nature of certain medical circumstances results in many devices used within close proximity to each other. Such configurations may have been considered by the manufacturer

as part of the design, but the ingenuity of device users to devise new systems may outstrip the manufacturer's expectations. Depending on the configuration and number of devices involved, hazards to the patient can result from the interference of one device with another, for example, electromagnetic interference. Even if the manufacturer intended for the device to be used in an environment with many others, patients can be at risk because of user behavior in dealing with the total amount of information that must be monitored. Again, developing appropriate problem-solving approaches depends on accurate problem identification.

Users may also attempt to interchange incompatible device components in an attempt at repair and create a risk to the patient. The use of nonapproved components not only can potentially create a hazard for the patient and user but also significantly reduces the reliability of the device.

12.5 RISK MANAGEMENT

Risk management is an ongoing process continually iterated throughout the life of a project. Some potential problems never materialize. Others materialize and are dealt with. New risks are identified, and mitigation strategies are devised as necessary. Some potential problems submerge, only to resurface later. Following the risk management procedures described here can increase the probability that potential problems will be identified, confronted, and overcome before they become crisis situations.

12.6 THE RISK MANAGEMENT PROCESS

Many projects fail to deliver acceptable systems within schedule and budget. Many of these failures might have been avoided had the project team properly assessed and mitigated the risk factors. Yet risk management is seldom applied as an explicit project management activity. One reason risk management is not practiced is that very few guidelines are available that offer a practical, step-by-step approach to managing risk.

The risk management process is a multistep process consisting of the following:

- Identifying the risk factors
- Assessing risk probabilities and effects on the project
- Developing strategies to mitigate identified risks
- Monitoring risk factors
- Invoking a contingency plan
- Managing the crisis
- Recovering from the crisis

A risk management process should be used throughout the development life cycle. The objective of the process is to manage risk so that it is both less than the maximum tolerable risk and also is ALARP. A typical risk management process is shown in Figure 12.2.

12.6.1 Identifying the Risk Factors

A risk is a potential problem. A problem is a risk that has materialized. Exactly when the transformation takes place is somewhat subjective. A schedule delay of 1 week might not be a cause for concern, but a delay of 1 month could have serious consequences. The important thing is that all parties who may be affected by a schedule delay agree in advance on the point at which a risk will become a problem. That way, when the risk does become a problem, it is mitigated by the planned corrective actions. In identifying a risk, one must take care to distinguish symptoms from underlying risk factors. A potential delay may in fact be a symptom of difficult technical issues or inadequate resources.

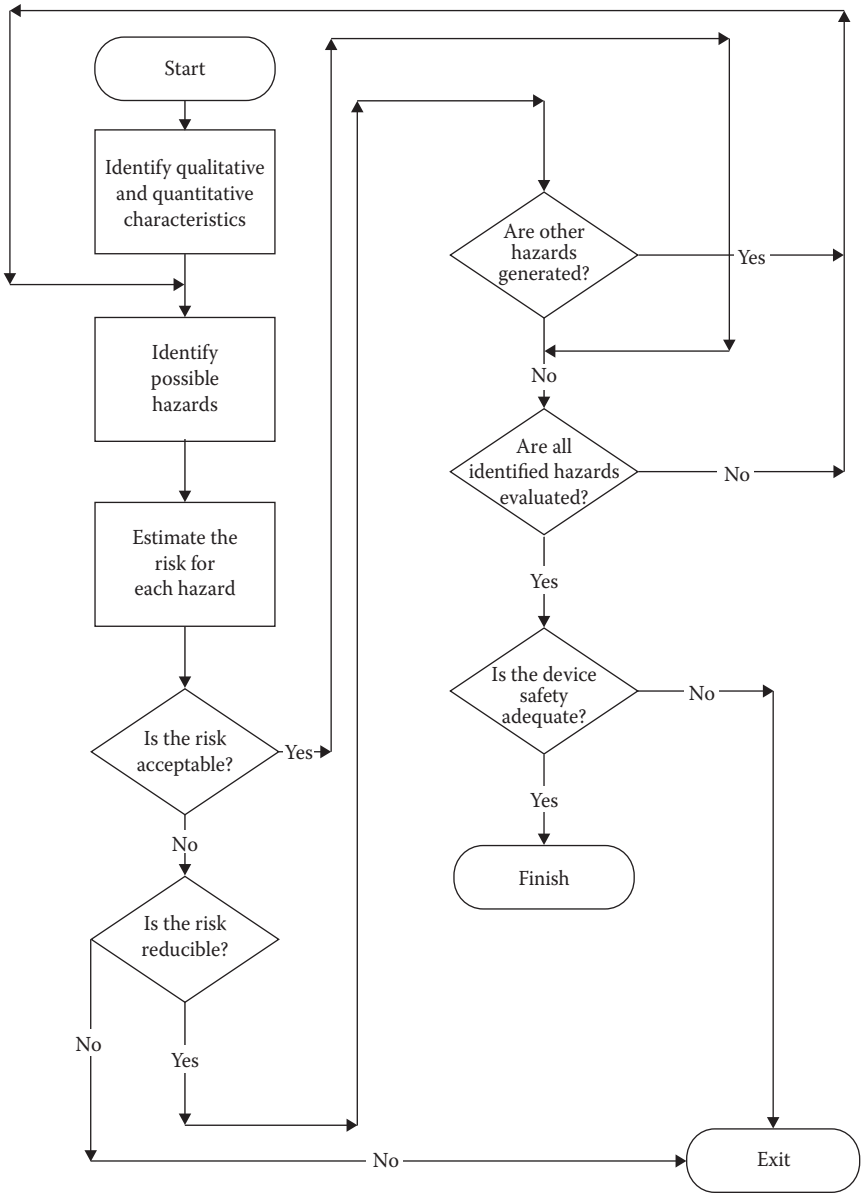

FIGURE 12.2 Typical risk management process.

Whether you identify a situation as a risk or an opportunity depends on your point of view. Is the glass half full or half empty? Situations with high potential for failure often have the potential for high payback as well. Risk management is not the same as risk aversion. Competitive pressures and the demands of modern society require that one take risks to be successful.

12.6.2 Assessing Risk Probabilities and Risks on the Project

Because risk implies a potential loss, one must estimate two elements of a risk:

- The probability that the risk will become a problem
- The effect the problem would have on the project's desired outcome

For most projects, the desired outcome is an acceptable product delivered on time and within budget. Factors that influence product acceptability include delivered functionality, performance, resource use, safety, reliability, versatility, ease of learning, ease of use, and ease of modification. Depending on the situation, failure to meet one or more of these criteria within the constraints of schedule and budget can precipitate a crisis for the developer, the customer, and/or the user community. Thus, the primary goal of risk management is to identify and confront risk factors with enough lead time to avoid a crisis.

12.6.3 Developing Strategies to Mitigate Identified Risks

In general, a risk becomes a problem when the value of a quantitative metric crosses a predetermined threshold. For that reason, two essential parts of risk management are setting thresholds, beyond which some corrective action is required, and determining ahead of time what that corrective action will be. Without such planning, one quickly realizes the truth in the answer to Fred Brooks' rhetorical question, "How does a project get to be a year late?" One day at a time.

Risk mitigation involves two types of strategies:

- Action planning
- Contingency planning

Action planning addresses risks that can be mitigated by immediate response. To address the risk of insufficient experience with a new hardware architecture, for example, the action plan could provide for training the development team, hiring experienced personnel, or finding a consultant to work with the project team. Of course, one should not spend more on training or hiring than would be paid back in increased productivity. If you estimate that training and hiring can increase productivity by 10%, for example, one should not spend more than 10% of the project's personnel budget in this manner.

Contingency planning, on the other hand, addresses risks that require monitoring for some future response should the need arise. To mitigate the risk of late delivery by a hardware vendor, for example, the contingency plan could provide for monitoring the vendor's progress and developing a software emulator for the target machine.

Of course, the risk of late hardware delivery must justify the added cost of preparing the contingency plan, monitoring the situation, and implementing the plan's actions. If the cost is justified, plan preparation and vendor monitoring might be implemented immediately, but the action to develop an emulator might be postponed until the risk of late delivery became a problem. This raises the issue of sufficient lead time. When does one start to develop the emulator? The answer lies in analyzing the probability of late delivery. As that probability increases, the urgency of developing the emulator becomes greater.

12.6.4 Monitoring Risk Factors

One must monitor the values of risk metrics, taking care that the metrics data are objective, timely, and accurate. If metrics are based on subjective factors, your project will quickly be reported as 90% complete and remain there for many months. One must avoid situations in which the first 90% of the project takes the first 90% of the schedule, while the remaining 10% of the project takes another 90% of the schedule.

12.6.5 Invoking a Contingency Plan

A contingency plan is invoked when a quantitative risk indicator crosses a predetermined threshold. One may find it difficult to convince the affected parties that a serious problem has developed, especially in the early stages of a project. A typical response is to plan on catching up during the next reporting period, but most projects never catch up without the explicit, planned corrective actions of a contingency plan. One must also specify the duration of each contingency plan to avoid contingent

actions of interminable duration. If the team cannot solve the problem within a specified period, typically 1 or 2 weeks, they must invoke a crisis-management plan.

12.6.6 Managing the Crisis

Despite a team's best efforts, the contingency plan may fail, in which case the project enters the crisis mode. There must be some plan for seeing a project through this phase, including allocating sufficient resources and specifying a drop-dead date, at which time management must reevaluate the project for more drastic corrective action.

12.6.7 Recovering from the Crisis

After a crisis, certain actions are required, such as rewarding personnel who have worked in burnout mode for an extended period and reevaluating cost and schedule in light of the drain on resources from managing the crisis.

12.7 TOOLS FOR RISK ESTIMATION

Several tools are helpful in conducting a risk estimation. These include the following:

- Hazard/risk analysis
- Failure modes and effects analysis (FMEA)
- Fault tree analysis (FTA)

12.7.1 Hazard/Risk Analysis

A hazard/risk analysis is the process, continuous throughout the product development cycle, that examines the possible hazards that could occur due to equipment failure and helps the designer to eliminate the hazard through various control methods. The hazard analysis is conducted on hardware, software, and the total system during the initial specification phase and is updated throughout the development cycle. The hazard analysis is documented on a form similar to that shown in Figure 12.3.

The following issues are addressed on the hazard analysis form:

• Potential hazard	Identifies possible harm to patient, operator, or system
• Generic cause	Identifies general conditions that can lead to the associated potential hazard
• Specific cause	Identifies specific instances that can give rise to the associated generic cause
• Premitigation potential	Classifies the likelihood of the associated probability hazard according to Table 12.4
• Premitigation severity	Categorizes the associated potential hazard according to Table 12.5
• Control mode	Means of reducing the probability and/or severity of the associated potential hazard
• Control method	Actual implementation to achieve the associated control mode
• Postmitigation probability	Categorizes the associated potential hazard according to Table 12.4 after the mitigation has been implemented
• Postmitigation severity	Categorizes the associated potential hazard according to Table 12.5 after the mitigation has been implemented
• Comments	Additional information, references, etc.
• Review comments	Comments written down during the review meeting

Hazard/risk analysis

Device:_____ Designer:_____ Date:_____

Potential hazard	Generic cause	Specific cause	Probability of occurrence	Severity level	Risk level	Control mode	Control method	Comments

FIGURE 12.3 Hazard analysis form.

TABLE 12.4
Classification of Probability of Occurrence

Probability	Occurrence	Details
1	Frequent	Likely to occur often
2	Occasional	Will occur several times in the lifetime of the device
3	Reasonably remote	Likely to occur sometime in the lifetime of the device
4	Remote	Unlikely to occur but possible
5	Extremely remote	Probability of occurrence indistinguishable from zero
6	Physically impossible	Probability of occurrence is zero

TABLE 12.5
Classification of Severity of the Hazard

Severity	Occurrence	Details
I	Catastrophic	Potential of resulting in multiple deaths or serious injuries
II	Critical	Potential of resulting in death or serious injury
III	Marginal	Potential of resulting in non–life-threatening injury
IV	Negligible	Little or no potential to result in non–life-threatening injury

12.7.2 Failure Modes and Effects Analysis Process

FMEA is initiated by selecting the lowest level of interest (usually the part, circuit, or module level) at which sufficient information is available. At this lowest level, the various failure modes that can occur for each item at that level are tabulated. The corresponding failure effect for each, taken singly and in turn, is interpreted as a failure mode for consideration of the failure effect at the next-higher functional level. Successive iterations result in the identification of the failure effects, in relation to specific failure modes, at all necessary functional levels up to the system or highest level.

The FMEA is documented on a form similar to that shown in Figure 12.4. The following issues are addressed on the FMEA form:

- Component — Name of the component under analysis
- Function — Function performed by the component in the system
- Failure mode — The specific failure mode
- Effect — The effect of the failure mode on the system
- Cause — The specific cause of the failure mode
- Severity — Categorizes the associated potential hazard according to Table 12.5
- Probability — Classifies the likelihood of the associated potential hazard according to Table 12.4
- Overall risk — Categorizes the overall risk of the failure according to Tables 12.6 and 12.7
- Comments — Additional information, references, etc.
- Review comments — Comments written down during the review meeting

Failure modes and effects analysis

Device:_____ Designer:_____ Date:_____

Component	Component function	Failure mode	Effect on failure	Cause of failure	Severity level	Probability of occurrence	Risk level	Comments

FIGURE 12.4 Failure modes and effects analysis (FMEA) form.

TABLE 12.6
Relationship of Occurrence to Severity of the Hazard

	Consequence			
Occurrence	**Negligible**	**Marginal**	**Critical**	**Catastrophic**
Frequent	II	I	I	I
Probable	III	II	I	I
Occasional	III	III	II	I
Remote	IV	III	III	II
Improbable	IV	IV	III	III
Incredible	IV	IV	IV	IV

TABLE 12.7
Interpretation of Risk Level

Risk Level	Interpretation
I	Intolerable risk
II	Undesirable risk, tolerable only if reduction is impractical or if the costs are grossly disproportionate to the improvement gained
III	Tolerable risk if the cost of risk reduction would exceed the improvement gained
IV	Negligible risk

12.7.3 Fault Tree Analysis

FTA is a "paper analysis" type of testing. Analysis starts by considering the various system modes of failures and working downward to identify the component cause of the failure and the probability of that failure. A fault tree is a logic diagram of a system that pictorially shows all probable failure modes and the sequence in which they occur, leading to a specified system failure. Since a logic flow process is used, standard logic and event symbols are used (Figure 12.5).

12.7.3.1 The FTA Process

FTA is a stepwise sequential process beginning with the collection of appropriate documentation for creating the fault tree. This documentation may include parts lists, operating environment requirements, a user manual, and so forth.

Once the documentation is reviewed, a failure is chosen that becomes the top event on the tree. This is the starting point for analysis and should be well defined and measurable. Where more than one top event can be identified, a separate fault tree should be conducted for each event.

Once this top event is identified, the fault tree can be developed. Branches from the top event are drawn to the events on the next level that could cause it. The secondary events are analyzed to determine if they are OR gates or AND gates or can be represented by an event symbol. The analysis continues downward until the lowest level is composed of basic fault events.

Once the tree is drawn, probability values are assigned to each gate or event. The quantification of the basic fault events can be derived from established sources of component failure rates, for example, MIL-HDBK-217, field use failure data, or vendor test data. Upper levels are calculated using the equations for the particular gates. Finally, the analysis is reviewed to determine where corrective action is necessary. Once corrective action is decided upon, action items are assigned and completion dates set. Following the review, a summary test report is issued.

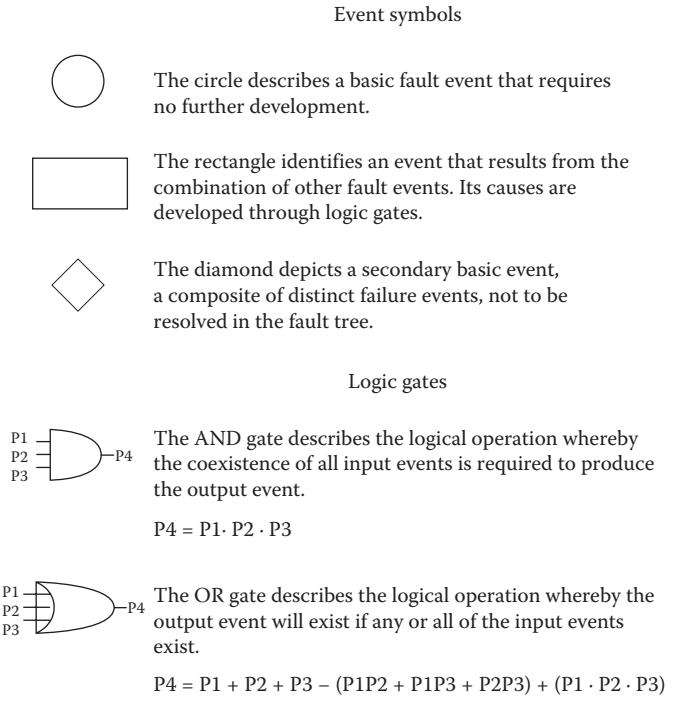

FIGURE 12.5 Logic symbols.

12.7.3.2 Example of an FTA

An alarm circuit (Figure 12.6) is to be analyzed. Components and their probability of failure are shown in Table 12.8.

The top event is chosen to be the lamp (C5) failing to light. The lamp would fail to light if

The switches failed to close
or
The source failed
or
The lamp and resistor failed

The next level of failures is chosen. The source fails if

The source fails
or
The emergency battery is ineffective

The lamp and resistor fails if

The bulb is defective
or
The resistor is defective

At the lowest level, the emergency battery is ineffective if

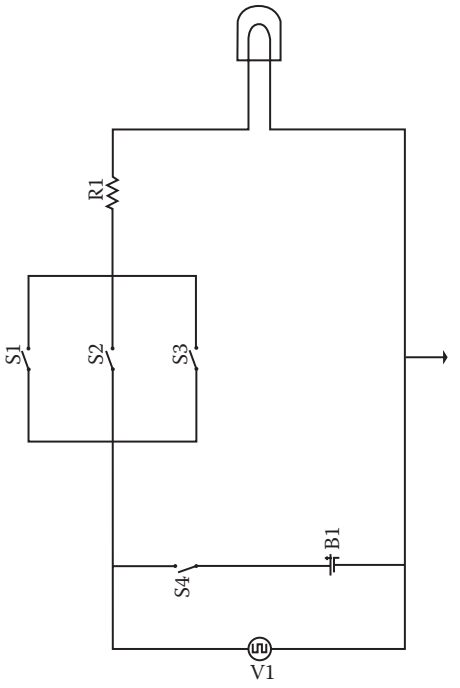

FIGURE 12.6 Alarm circuit.

TABLE 12.8
Components and Their Probability of Failure

Component	Designation	Failure Probability
Voltage source	V1	0.01752
Switch	S4	0.00438
Battery	B1	0.03679
Switch	S1	0.00438
Switch	S2	0.00438
Switch	S3	0.00438
Resistor	R1	0.00263
Lamp	L1	0.00876

The switch fails to close
or
The battery is dead

Figure 12.7 shows the fault tree for the circuit.

Once the fault tree is developed, the probabilities for each level can be entered in a probability tree and the probability of failure for the top event calculated, using the equations for the gates. Figure 12.8 shows the probability tree for the alarm circuit.

12.8 RISK ANALYSIS AND SYSTEMS

The Accreditation Board for Engineering and Technology (ABET) requirements for design state, "Students must be prepared for engineering practice through the curriculum culminating in a *major*

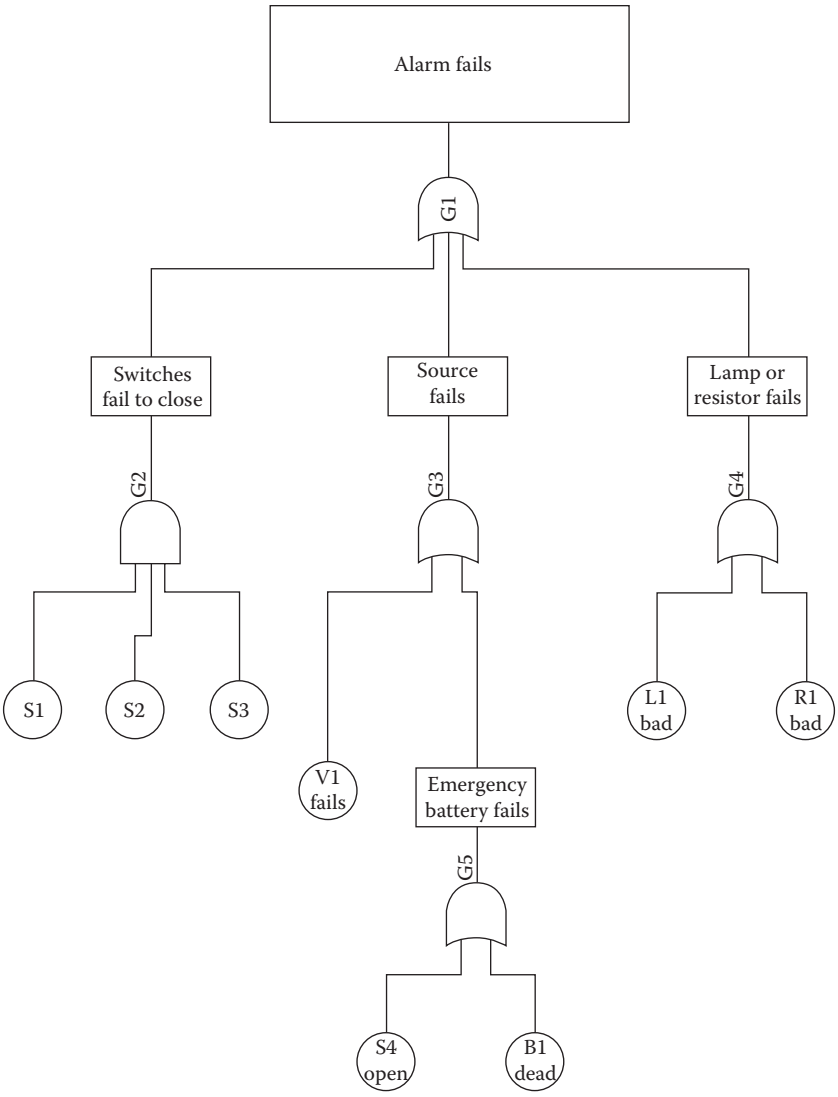

FIGURE 12.7 Failure Modes Diagram.

design experience based upon the knowledge and skills acquired in earlier coursework and incorporating engineering standards and realistic constraints that include most of the following considerations: economic; environmental; sustainability; manufacturability; ethical; health and safety; social; and political" (from the ABET website, www.abet.org). That biomedical engineering design work would involve health aspects is obvious. The several aspects involving safety and the potential for liability require a discussion of the need for safety considerations in the design and redesign of medical devices and in somewhat similar activities in process design.

The recently published National Academy Press publication "To Err Is Human: Building a Safer Health System"[1] has provided several notable statistics, specifically, "The human cost of medical errors is high. Based on the findings of one major study, medical errors kill some 44,000 people in U.S. hospitals each year. Another study puts the number much higher, at 98,000. Even using the lower estimate, more people die from medical mistakes each year than from highway accidents, breast cancer, or AIDS." This statistic permits comparing medical error deaths to the number of deaths due to other accidental causes, such as may be found from the National Safety Council

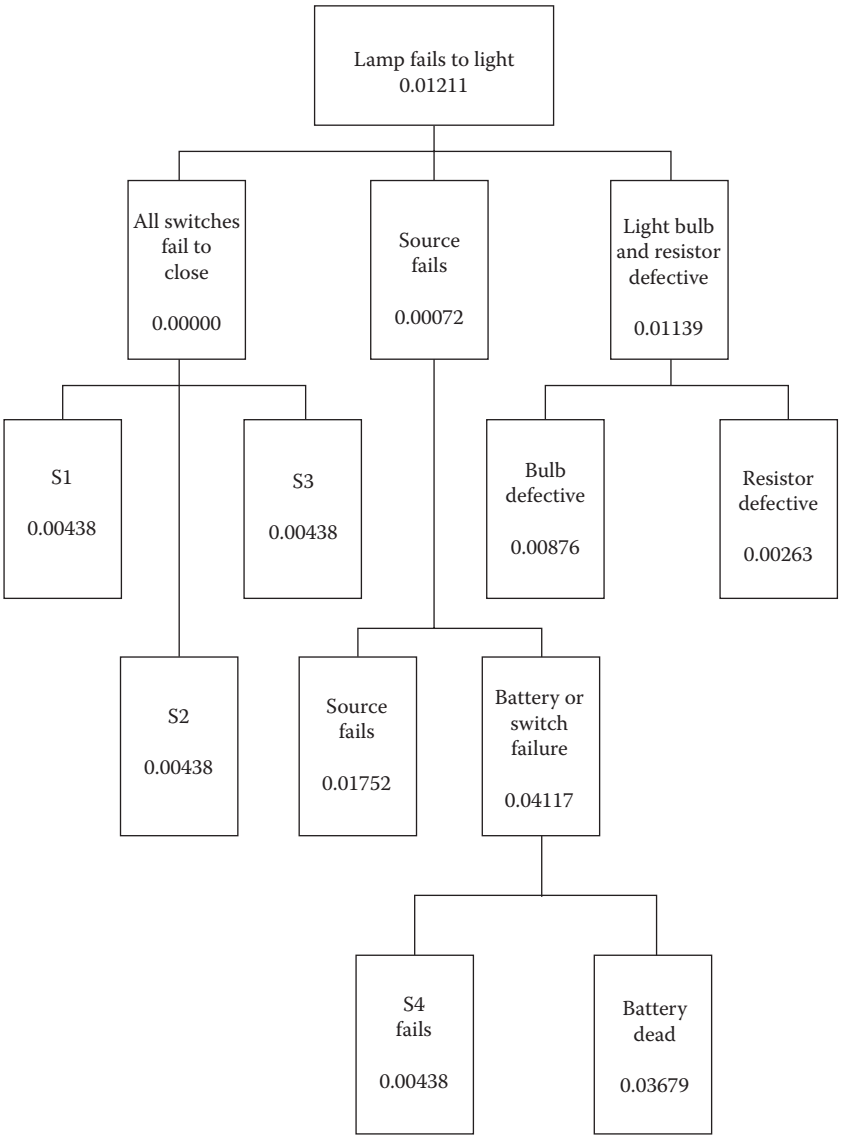

FIGURE 12.8 Probability tree.

website (www.nsc.org), and to the number of deaths due to specific diseases. The safety council data estimates 150,445 total deaths due to injuries in 1998, a statistic on par with the aforementioned. The magnitude of the aforementioned numbers should impress one as to the need for safety considerations, not just for public activities but also for medical activities, such as those involved in the design of medical devices and systems.

12.8.1 Medical Case Example

Let us illustrate the previous discussion with an example based upon an actual event. A young Down's syndrome patient with multiple heart defects died from an air embolism during a preoperative

cardiac flow/oxygenation catheterization study. Evidence acquired from the hospital involved the following data and devices:

- The medical record for the patient.
- Testimony regarding the procedure.
- Complete records of blood pressure and electrocardiogram (EKG) as various sites were checked for pressures and sampled for oxygen saturation levels; blood pressure was sampled periodically using the system described later.
- The catheterization system, which included a three-port connection system (manifold) for blood pressure determination, saline infusion, and blood sampling/injection via a syringe.
- A typical saline bag and connector assembly.
- An opaque pressurization jacket used to pressurize the saline bag to ensure saline flow when the saline port was opened.

There are two items to be determined at this point. It is a given that the patient died of an air embolus. How this occurred and what could have been done to prevent this are two of the questions to be asked. Let us ask the second first, discussing some of the general procedures that must be used to analyze safe devices and procedures.

12.8.2 Safety in Design

Good design practices should consider means by which a given design may cause harm, and they should—via guide sentences, structure, or checklists—assist the designer in determination of improvements to the system under study. Let us illustrate this with another example: Drink machines have been known to tip over and kill or maim persons shaking them when irate over nondelivery of drinks (a few deaths per year in the United States). How can this be prevented?

A quick checklist can be found that helps one begin the solution to this problem; this checklist can read as the following (from the program *designsafe*, from Designsafe Engineering):

- Eliminate by design
- Guard against
- Warn the user
- Train the user
- Mandate the use of personal protective equipment
- Other

As the drink machine manufacturer, what solutions are possible here? Mandating that the user wear protective equipment is not likely, nor is training the user. One might warn the user to not tilt the drink machine in order to get a drink, but it is not likely that you would win a case involving the death of a user due to your machine. Guarding against the machine tilting would seem to be a better approach; strapping the machine to a nearby wall should enable this outcome. A far better approach would be to eliminate the problem by design by placing the weight of the unsold drinks at the base of the machine, rather than at the top (which enables gravity feed of the drinks and thus a cheaper design).

The previous checklist is simply an outline; in practice, each of the subheadings can have various gradations. For example, the warning of the user can be visual or audible, color coded, flashing, and so forth.

Implied in the previous discussion are a few other concepts that are mandatory to understand if one is to analyze unsafe designs. One is the term *hazard*, which may be defined as a source of potential harm or a situation with a potential for harm. Another is *risk*, which is a combination of the probability of occurrence of harm and the severity of that harm. If you as the manufacturer of the aforementioned machine decide to not redesign anything, you are apparently assuming that your risk of financial harm due to a lawsuit is less than your cost to prevent the problem in the first

place. Good design practices will include hazard analysis and risk assessment at every stage of the design, with an ultimate goal of risk and potential liability reduction. As safe design is mandated for medical devices by the FDA, this practice must be documented as a device is developed. As the variety of users in the medical environment is so varied in terms of education and responsibilities and other tasks, good design must involve a fairly comprehensive list of items.

Let us once again use the drink machine example to look at this process of safe design. A typical approach to an analysis could include the following steps:

- Identify users (for example, drink installer, general public).
- Identify hazards each user may be subjected to; this hazard list is associated with a checklist such as mechanical hazards, chemical, health, and so forth. (Mechanical problems would be paramount here.)
- Begin the risk assessment, using a guide sentence such as "When doing the (task), the hazard may cause (harm)." One of the guide sentences here would be "When shaking the machine, it could tip and crush the user."
- Identify the severity of the harm (catastrophic, serious, slight, minimal); the exposure to harm (frequent, occasional, remote, none); and the probability of harm (probable, possible, unlikely, negligible) and therefore the risk level (high, moderate, low). A high risk level implies the outcome of severe to moderate injury or death, moderate implies moderate to low probability of harm, and low implies moderate to mild injury. The risk of death from an unsecured drink machine falling on one is high, and the exposure is remote (it does happen!); the probability of it occurring with an untethered machine is high.
- The complete analysis would then involve the identification of methods to reduce the risk (such as guarding), the revised exposure and risk data, and the personnel in charge of this activity.

Special attention should be given to situations where the device may be misused in order to "cover all bases" in an analysis. Additionally, especially in the case of devices used in a clinical environment, special consideration should be given not only to the primary users of the device but also to casual users (cleaning crew) and special-needs patients (elderly, very young, very ill, AIDS, at risk, etc.). Human factors analyses should also be considered, especially in light of situations where there might be high stress on the part of the user (see Chapter 9).

12.8.3 Medical Case Example—Revisited

Let us revisit the case mentioned regarding the death of a young Down's syndrome child with multiple heart defects. What considerations should there be in this case—regarding instrumentation, risk, and fault? The following are a few of the points to consider when looking at this case:

- The patient was described as young. A far smaller amount of air can cause death from air embolism in young patients as compared to adults—children are more "at risk" for this problem compared to adults.
- Down's syndrome children often have heart problems; this particular patient was described as having multiple heart defects. Heart shunts predispose patients to risks from air emboli; this patient had shunts (the reason for the study and determination of oxygenation levels).
- The diagnosis was that the patient died of an air embolus. Where did the air come from?

The solution to this case (as a legal case) lies in determining how the air got into the patient. How can this be used to redesign the process or the mentioned devices to ensure that this does not happen again? The answer lies in application of good safety engineering principles.

The particular hazard being addressed in this discussion is one of several that accompany this type of diagnostic workup, but let us address only this one concern (the air). The hazard to be investigated

is a dramatic decrease in the ability of the heart to pump blood due to the inadvertent introduction of air into the patient. How could air get into the patient? A few of the ways include the following:

1. Air entering the patient through the catheter insertion point in the groin
2. Air entering the patient via a medication line
3. Accidental opening of the blood pressure sensor port, suction of air into the patient
4. Flushing of the blood pressure sensor port with air, rather than saline
5. Accidental infusion of air from the surgeon's sampling syringe, rather than sampling of blood at this site
6. Infusion of air from the saline drip bag

Five of these were eliminated very quickly based upon the medical records in the case. The patient was supine; thus the risk of number 1 was minimal. Even if air had been inserted at this point, the likelihood of damage was minimal. Medication lines were patent; there was no evidence of air in them. Suction of air into the patient due to an opened pressure sensor line was unlikely; the pressures recorded in the patient at all sites were positive with respect to atmospheric, with only a few milliseconds per beat occasionally becoming subatmospheric (insufficient time to cause air to enter). Number 4 is not likely; had it occurred, only a syringe full of air could have been injected (10 mL or so). It is not likely that the air could have made it to the patient. Number 5 is unlikely also; again, the dose of air would have been 10 mL maximum (this has happened). The implication is that air from the infusion bag, due to the pressurizing jacket, entered the patient. For the particular 1 L bags in use, there is about 35 mL of air, an amount adequate to cause death in a young at-risk patient. The pressurization bag ensured that the air was indeed pumped to the patient. A simulation of the situation showed that this could occur in less than 5 seconds at the measured pressures involved—too quick if one was otherwise involved with measuring data from the patient!

Why is there air in the infusion bag? To ensure that—when drugs are injected into the bag—mixing can occur by shaking the bag. What would have been a safe design for this situation? Simply elect to *not* use a pressurization jacket.

A counterargument may occur here, once one realizes that the air in such a bag ensures that drugs, when injected into the bag through one of the ports, cannot be properly mixed unless there is air in the bag (and the bag is shaken properly).

12.8.4 Process Improvement

The prior discussion on the air embolism was successful in determining the cause of the death through asking the question "How did the air get into the patient?" There are several other methods the reader will find useful in determining "fault" or "cause" of an untoward event. One such method simply uses the question "why" enough times that the questioner, assuming that there are answers to each of the more in-depth "why" questions, finally gets at the root cause of an event.

Most hospitals have a safety process in place that looks for methods to improve the processes of health care delivery. This group may operate with the name of quality improvement, quality assurance, patient safety committee, or the like. Some of the processes involved in their work involve the types of analyses just discussed, some of their work involves flowcharting (see Chapter 2), and some involves the use of cause-and-effect diagrams. Figure 12.9 illustrates the use of this concept using an Ishikawa or "fishbone" diagram. This particular diagram was generated to look at the process for "bad infusion outcomes" to assist in identifying the potential cause of this outcome (provided by Dr. Doris Quinn, Nashville, TN: Vanderbilt Quality Assurance Department). In a major brainstorming session, the chart was first generated by considering the major items involved in the process of generating an infusion process, namely, people who give the infusion, written policies regarding protocol for this infusion, the patients involved, and the "equipment" involved in the process. Each "bone" coming off of these four main "bones" relates to some attribute of the main section that might have an influence on outcomes. For example, a root

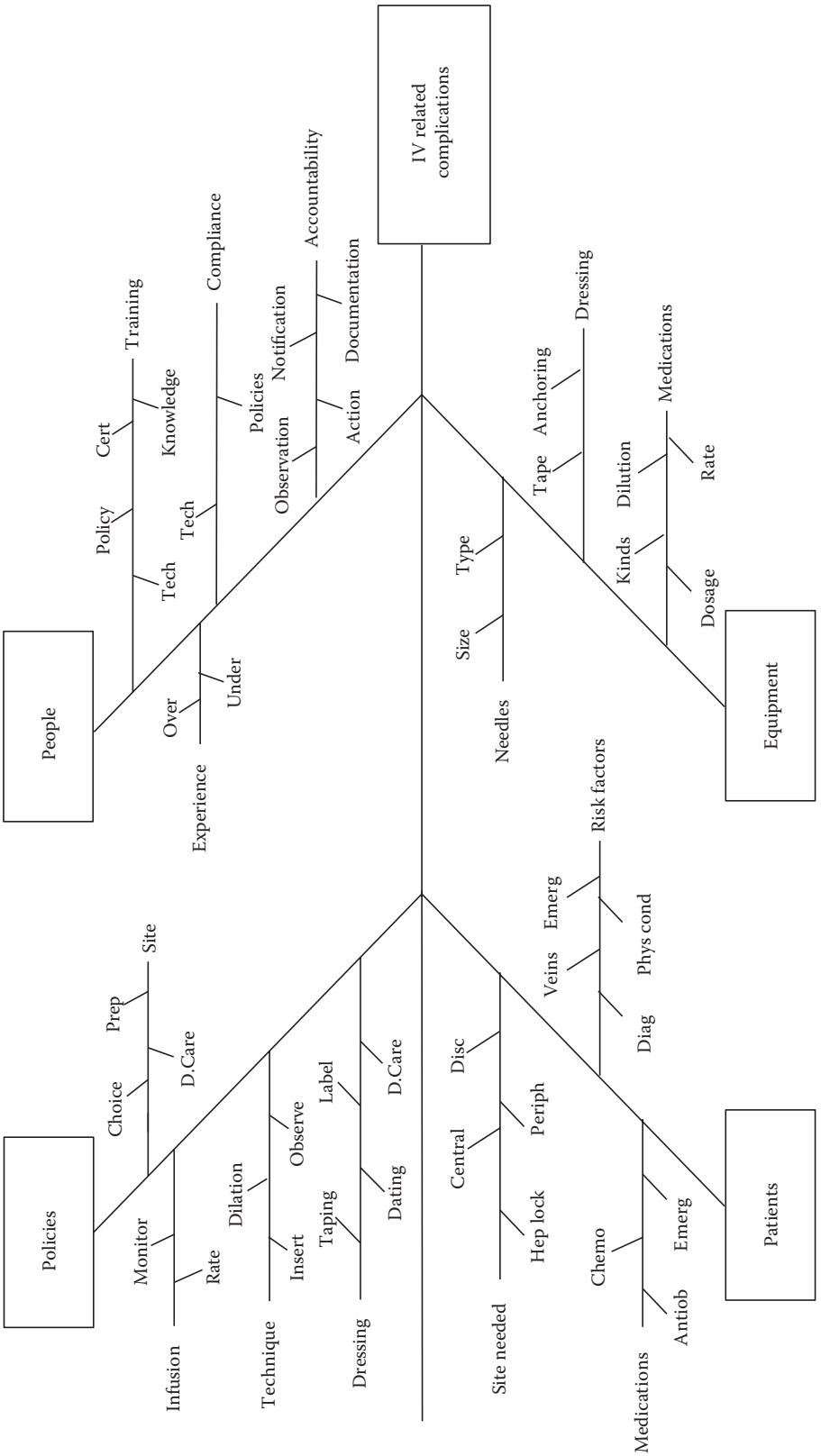

FIGURE 12.9 Causes and effect diagram, IV complications.

cause of IV-related complications might be that the people giving the IV may be underexperienced. Similarly, the antibiotic that the patient may be taking may be interfering with the IV, and so forth.

Once such a chart is completed, one can study each of the potential "root causes" of the outcome and try to determine which one (or ones) might have caused the outcome. Of interest is the fact that while the administration was asking for additional in-service training for personnel doing infusions (to counter an underexperienced person), this particular chart was of value in identifying the real cause of the problem, a change in the supplied concentration of the drug in question.

This technique is useful for analysis of problems in multiple areas, such as processes (here), manufacturing, management, and services.

12.8.5 Miscellaneous Issues

Major design problems in some devices and drugs have resulted from drug interactions and materials failures. The need for both animal and human testing for drug interactions and possible materials testing for implanted materials serves as a beginning point for discussions of these topics. Much of this testing is mandated by the FDA in terms of required test protocols. Specifically, the drug thalidomide and some of the early experiences with heart valves deserve mention in discussions on historical problems, many of which are covered in the references cited here.[2–4] A discussion of patent medicines and quack medical devices, with their inherent risks to human safety, are addressed in some websites (http://www.cyberus.ca/~sjordan/pmmain.htm and http://www.mtn.org/quack).

12.9 OTHER PROCESS ISSUES

Many of the mistakes made in the hospital environment are due to communication issues. Redesign of hospital systems should pay special attention to the interfaces between people, with an emphasis on correct communication. To this end, computerization of drug and medication dosing should be stressed, avoiding all oral transfers of information if at all possible. Double-checking of doses and allergies to medicines can help alleviate many medication errors. Double-checking of drug interactions via computer, and the alerting of the health care provider to this possibility, is of value also. With an average of 18 or so medications per patient in a large hospital, this is of high importance. Both private and governmental (e.g., the Veterans Administration [VA] and Department of Defense) agencies are pursuing electronic medical records. Medicines and most equipment will likely be bar-coded in the near future to enable accurate input of this information without keystroke errors.

Governmental influences will also have an effect on improving health care. A long-overdue policy on the part of the FDA is the ending of soundalike and lookalike medication names by fiat. The U.S. government, through the Department of Health and Human Services, has established the Agency for Healthcare Research and Quality (www.ahrq.gov), which is funding several initiatives on improving the quality of health care. A specific aim includes the use of evidence-based decision making. The AHRQ will be the lead agency in setting up a system for reporting of medical errors and the analysis thereof. The AHRQ has set up a system for classifying and counting patient safety incidents. Such incidents include the terms "failure to rescue," "decubitus ulcer," and "postoperative sepsis." The use of such indicators on data derived from patient safety reporting from organizations has led to a system to rank and evaluate and recommend changes in techniques among various hospitals and practitioners. The AHRQ is a research-based organization and, as such, will affect medical care based upon the quality of the evidence-based research it performs and sponsors.

Figure 12.10 is an example of the type of data that might be presented in making a case for specilized studies sponsored by the AHRQ. It, as presented here, is a histogram of "patient incidents" (fabricated data) versus incident type. The particular ordering of incidents of high value to low value allows one to study the impact (lost lives, lost incomes, etc.) of solving one or more problems. Histograms arranged in this particular order, sometimes with an overlaid percentage of total line (left to right, with 0–100% scale on the right), are termed Pareto charts.

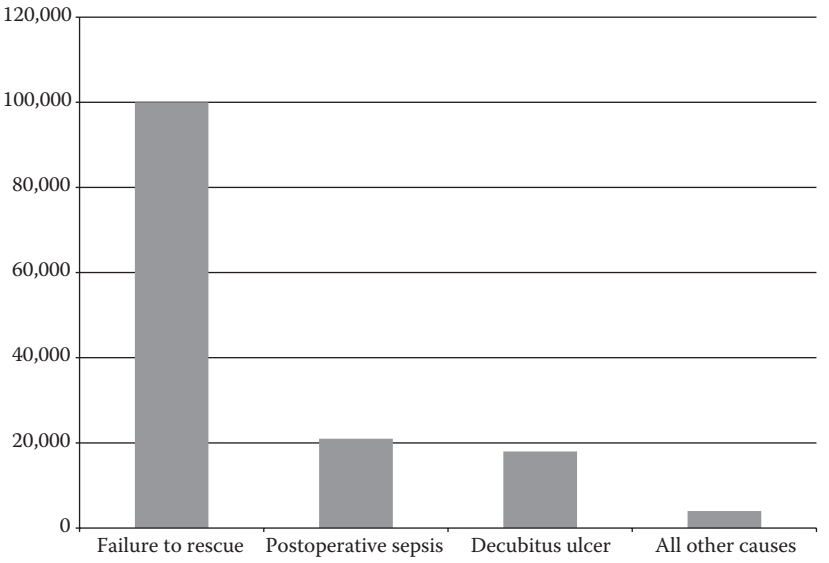

FIGURE 12.10 Histogram of safety incidents.

The Joint Commission (once the Joint Commission on the Accreditation of Health Care Organizations) has sponsored a National Patient Safety goals and requirements program since 2003. Specific goals include such items as increasing the accuracy of patient identification and recognition and response to changes in a patient's condition, health care worker fatigue and its potential effect on care, and so forth. As this is the major accreditation agency in the United States for health care organizations and programs, this group has a strong voice in standards setting and potential improvements.

The National Institute for Occupational Safety and Health (NIOSH) sponsored a "Prevention through Design" workshop in 2007, with the aim of setting up a national group to look at the "designing out" of possibilities for injury via better product and process design. This group also has a health care contingent.

Private foundations also interested in improving patient safety include the National Patent Safety Foundation (www.npsf.org) and the Robert Wood Johnson Foundation. One of the interesting outcomes of the Johnson Foundation group (and others) is the LeapFrog Group, which calls for improved health care decisions and the use of incentives and rewards for providers.

12.9.1 Summary

Designing with safety in mind is mandatory. Appropriate design for safe and effective devices and processes may cost more in the initial design but should pay continuing benefits in the long run. Health care should be safe, equitable, effective, patient centered, timely, efficient, and equitable.[5] Note that the first term is *safe*.

EXERCISES

1. Visit a site such as www.designsafe.com; download the demo version of the software.
2. Perform a risk analysis of your design project or one of your instructor's choosing.
3. Visit the FDA MAUDE site; do a search for any device that caused a death in the past 2 months. Perform a safety analysis on this device.
4. Visit the FDA MAUDE site; do a search for any device that caused an accidental injury in the past few months. Discuss the harm caused and the possible correction of this problem.
5. There are several variations on safety analyses. Define and discuss FMEA and its applications to medicine.

6. Do a search for the term "anticipatory failure determination" and report on the value of this type of software.
7. Develop a cause-and-effect diagram for the air embolus case discussed in this chapter.
8. Search for information on thalidomide; discuss what went wrong with the use of this drug. Find and discuss at least one other drug example.
9. Some of the early heart valves had mechanical problems. Discuss how this is not a likely event today.
10. Search for information on the failure rate of implant pumps for the alleviation of male erectile dysfunction. What design problems occurred in these devices?
11. Major accidents sometimes cause a rethinking of basic procedures. Investigate the major accident at Bhopal and some of the recommendations that arose from this event.
12. Find and describe the specific wording that requires safety in medical devices, both for the FDA and for CE marking.
13. Read and report on one relevant chapter from Geddes (*Medical Device Accidents*) or Casey (*Set Phasers on Stun*). (See references 7 and 8.)
14. Do a search and report on the term "inherently safer design."
15. Discuss the necessary components of a system to guarantee a proper patient–blood transfusion match.

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13 Testing

> Building technical systems involves a lot of hard work and specialized knowledge: languages and protocols, coding and debugging, testing and refactoring.
>
> **Jesse J. Garrett**

Testing may be defined as subjecting a device to conditions that indicate its weaknesses, behavior characteristics, and modes of failure. It is a continuous operation throughout the development cycle that provides pertinent information to the development team. Testing may be performed for three basic reasons:

- Basic information
- Verification
- Validation

Basic information testing may include vendor evaluation, vendor comparison, and component limitability. Verification is the process of evaluating the products of a given phase to ensure correctness and consistency with respect to the products and standards provided as input to that phase. Validation includes proving that the subsystems and the system meet the requirements of the product specification.

Testing is an essential part of any engineering development program. If the development risks are high, the test program becomes a major component of the overall development effort. To provide the basis for a properly integrated development test program, the design specification should cover all criteria to be tested including function, environment, reliability, and safety. The test program should be drawn up to cover assurance of all these design criteria.

The ultimate goal of testing is assuring that the customer is satisfied. It is the customer who pays the bills, and if we are to be successful in business, we have to solve their problems. We aim for quality, but quality is not just an abstract ideal. We are developing systems to be used, and used successfully, not to be admired on the shelf. If quality is to be a meaningful and useful goal in the real world, it must include the customer.

13.1 TESTING DEFINED

Definitions matter, although consensus as to what testing really is is less important than being able to use these definitions to focus our attention on the things that should happen when we are testing. Historically, testing has been defined in several ways:

- Establishing confidence that a device does what it is supposed to do
- The process of operating a device with the intent of finding errors
- Detecting specification errors and deviations from the specification
- Verifying that a system satisfies its specified requirements or identifying differences between expected and actual results
- The process of operating a device or component under specified conditions, observing or recording the results, and making an evaluation of some aspect of the system or component

All these definitions are useful but in different ways. Some focus on what is done while testing, others focus on more general objectives like assessing quality and customer satisfaction, while others focus on

goals like expected results. If customer satisfaction is a goal, this satisfaction, or what would constitute it, should be expressed in the requirements. Identifying differences between expected and actual results is valuable because it focuses on the fact that when we are testing, we need to be able to anticipate what is supposed to happen. It is then possible to determine what actually does happen and compare the two.

If a test is to find every conceivable fault or weakness in the system or component, then a good test is one that has a good probability of detecting an as-yet undiscovered error, and a successful test is one that detects an as-yet undiscovered error. The focus on showing the presence of errors is the basic attitude of a good test.

Testing is a positive and creative effort of destruction. It takes imagination, persistence, and a strong sense of mission to systematically locate the weaknesses in a complex structure and to demonstrate its failures. This is one reason why it is so hard to test our own work. There is a natural real sense in which we do not want to find errors in our own material.

Errors are in the work product, not in the person who made the mistake. With the "test to destroy" attitude, we are not attacking an individual in an organization or team of developers but, rather, are looking for errors in those developers' work products.

Everyone on the development team needs to understand that tests add value to the product by discovering errors and getting them on the table as early as possible—to save the developers from building products based on error-ridden sources, to ensure that the marketing people can deliver what the customer wants, and to assure that management gets the bottom line on the quality and finance they are looking for.

13.2 PARSING TEST REQUIREMENTS

No matter what type of test is conducted, there are certain requirements that must be proven as a result of the test. Before testing begins, it is helpful to place all requirements into a database where they may be sorted on a variety of attributes, such as responsible subsystems. The purpose of the database is to assure that all requirements are addressed in the test protocol as well as providing a convenient tracking system for the requirements. Where the number of requirements is small, manual collation of the requirements is effective. Where the number of requirements is large, the use of a software program to parse requirements is most helpful. Parsed requirements are placed in a database, including the following:

- Requirement number (among all requirements)
- Statement of requirement
- Paragraph number in the document that contains the requirement
- Requirement number within that paragraph
- Author of the requirement
- Team responsible for ensuring that the requirement is addressed
- Type of test to address the requirement

The database is also a great indicator to inspectors that the design team is well organized and responsible. The following is an example of a parsing database.

Req #	Requirement	Paragraph Number	Req # in Paragraph	Author	Requirement Responsibility	Test Type
1221	The machine shall contain no burrs or sharp edges	3.1	1	Smith	System	Visual
1222	The maximum height of the machine shall be 175 cm	3.1	2	Smith	System	Validation
1223	The power supply shall have a maximum inrush current of 7.3V	3.2	1	Jones	Subsystem B	Verification

TABLE 13.1
Requirements Checklist

Requirement	Requirement Number	Document Location	Protocol Location	Results Location	Initials of Tester	Test Date
The unit must operate according to specification after exposure to an ambient temperature of 65°C	12	Product specification of paragraph 10.2.1	Lab notebook # R323, page 44	Lab notebook # R323, page 45–46	*JR*	6/12/96
The unit must operate according to specification after exposure to an ambient temperature of –40°C	13	Product specification of paragraph 10.2.2	Lab notebook # R323, page 47	Lab notebook # R323, page 48–49	*JR*	6/15/96
The unit must operate according to specification after exposure to an ambient temperature of 40°C and a relative humidity of 95%	14	Product specification of paragraph 10.2.3	Lab notebook # R323, page 54	Lab notebook # R323, page 55–57	*JL*	7/13/96

Once the requirements are listed, they can be used to develop the various test protocols necessary for testing. In addition, the list of requirements can be made more useful by turning them into a checklist, as seen in Table 13.1, by adding space for additional information, such as reference to the location of a particular requirement, location of the test protocol, location of the test results, the initials of the person performing and completing the test, and the date of test completion. This checklist is also invaluable in tracking all requirements to satisfy quality assurance and regulatory departments as well as Food and Drug Administration (FDA) and International Standards Organization (ISO) auditors.

13.3 TEST PROTOCOL

It has been said that testing without a plan is not testing at all but an experiment. Therefore, it is essential that each test performed be detailed in a test protocol that includes the following:

- The name of the device under test
- The type of test being performed
- The purpose of the test
- A definition of potential failures during the test
- Any special requirements
- The number of units on test
- The length of the test in hours or cycles
- A detailed procedure for running the test or reference to a procedure in another document, such as a standard
- The parameters to be recorded

13.4 TEST METHODOLOGY

Types of testing may include time testing, event testing, stress testing, environmental testing, time-related testing, and failure-related testing.

13.4.1 Time Testing

Time testing is conducted primarily to determine long-term reliability parameters, such as failure rate and mean time between failures (MTBF). Time testing can also be conducted to determine what part or component fails, when it fails, the mode of failure at that particular time, the mechanism of failure, and how much more or less life the equipment has that is required for operational use. This allows priorities of criticality for reliability improvement to be established.

13.4.2 Event Testing

Event testing consists of repeated testing of equipment through its cycle of operation until failure. This type of testing is analogous to time-to-failure testing. One important parameter developed from this type of test is the number of cycles to failure.

13.4.3 Stress Testing

Stress testing has an important place in reliability assessment, but care must be taken in its application. Too much overstress may cause the test results to be inconclusive, as overstress may precipitate a failure that the product would not normally experience during normal usage. Care should also be taken to overstress in steps, rather than getting to the maximum value immediately. If the device fails, the step method allows the determination of where in the progression the failure occurred.

TABLE 13.2
Environmental Testing Standards

Environment	Applicable Standard
Operating temperature	IEC 68-2-14
Storage temperature	IEC 68-2-1
	IEC 68-2-2
Operating humidity	IEC 68-2-30
Storage humidity	IEC 68-2-3
	IEC 68-2-30
Operating ambient pressure	IEC 68-2-13
Storage ambient pressure	IEC 68-2-13
Transportation	NSTA
Radiated electrical emissions	CISPR 11
Radiated magnetic emissions	VDE 871
Radiated electrical field	IEC 601-1-2
Electrical fast transient	IEC 601-1-2
Radiated magnetic immunity	IEC 1000-4-8
Line conducted immunity	IEC 1000-4-6
Operating vibration	IEC 68-2-6
	IEC 68-2-34
Unpackaged shock	IEC 68-2-27
Stability	UL 2601
Ingress of liquids	IEC 529
	IEC 601-1
Pneumatic supply	CEN-TC215

13.4.4 Environmental Testing

Environmental testing represents a survey of the reaction of a device to the environmental and shipping environments it should experience in its daily usage. By investigating a broad spectrum of the environmental space, greater confidence is developed in the equipment than if it was merely subjected to ambient conditions. As with overstress testing, avoid unusually extreme or unrealistic environmental levels because of the difficulty in their interpretation. Table 13.2 lists some typical environmental tests and the standard associated with its execution.

13.4.5 Time-Related Testing

Time-related testing is conducted until a certain number of hours of operation or a certain number of cycles has been completed, for example, a switch test conducted for 100,000 ON/OFF cycles or a monitor operated for 100,000 hours. This type of test will be important in choosing the correct formula to calculate MTBF from the test data.

13.4.6 Failure-Related Testing

A test may be conducted until all test units or a certain percentage of units have failed, for example, ventilators operated until the first unit fails or power supplies power-cycled until all have failed. This type of test will be important in choosing the correct formula to calculate MTBF from the test data.

13.5 PURPOSE OF THE TEST

The purposes for testing may include the feasibility of a design, comparing two or more vendors, comparing two or more configurations, testing the response to environmental stresses, developing reliability parameters, failure analysis, or validation of the device.

All testing, except the reliability demonstration, which is performed at the end of the product development cycle, is normally performed at a confidence level of 90%. This means that one is 90% confident that the reliability parameters established in the test will be characteristic of units in the field. A 90% confidence level also yields a risk factor of (1 − confidence level) or 10%. The reliability demonstration should be conducted at a confidence level of 95%, giving a risk factor of 5%. These levels will be important in determining the number of test units and the length of test time.

13.6 FAILURE DEFINITION

For each test and for each device, a failure must be defined. This definition depends on the intended application and the anticipated environment. What is considered a failure for one component or device may not be a failure for another. The test protocol should be as detailed as possible in defining the failure.

13.7 DETERMINING SAMPLE SIZE AND TEST LENGTH

Once you determine the type of test to be performed, you need to decide on the test sample size and the length of time necessary to accomplish your testing goal. Sample size and test time are dependent upon the MTBF goal, originally defined in the product specification, and on the confidence level at which the test will be conducted.

The formula for determining the sample size and test time is derived from the following equation:

$$\text{MTBF goal} = (\text{sample size})(\text{test time})(2)/X^2_{\alpha;2r+2} \tag{13.1}$$

The equation thus becomes

$$(\text{Sample size})(\text{test time}) = \text{MTBF goal}\left(X^2_{\alpha;2r+2}\right)/2 \tag{13.2}$$

To complete the equation, we must first understand the χ^2 chart, included in Appendix 1. To use this chart, first find the risk factor that the chart is based upon. As mentioned earlier, the risk factor is derived from the confidence level:

$$\text{Confidence level} = 1 - \alpha$$

where α is the risk factor.

Thus, a confidence level of 90% yields a risk factor of 10%, while a confidence level of 95% yields a risk factor of 5%. Using the 90% confidence level, $\alpha = 0.10$ in Equation 13.2.

The r in Equation 13.2 is the number of failures. When calculating sample size and test time, it is assumed that there will be no failures. This results in the minimal test time. Thus, $r = 2(0) + 2$ or 2, and Equation 13.2 becomes

$$(\text{Sample size})(\text{test time}) = \text{MTBF goal}\left(X^2_{\alpha;2}\right)/2$$

Looking at the χ^2 chart in Appendix 1, go across the top row of the chart and find 0.10, or *. Go down that column to the line for $v = 2$. There you will find the number 4.605, or 4.61. Put this into the equation:

$$(\text{Sample size})(\text{test time}) = \text{MTBF goal}\,(4.61)/2 \tag{13.3}$$

Inserting the MTBF goal into the equation and solving it yields the unit test time or (sample size) (test time).

Example 13.1

We want to test some power supplies to prove an MTBF goal of 50,000 hours of operation. How many units do we test and for how long, assuming no failures?

$$\begin{aligned}(\text{Sample size})(\text{test time}) &= \text{MTBF goal}\,(4.61)/2\\ (\text{Sample size})(\text{test time}) &= 50{,}000\,(4.61)/2\\ &= 115{,}250\ \text{unit-hours}\end{aligned}$$

From these data, we can calculate the possibilities listed in Table 13.3. These data are based on the statistical law that states that 1 unit tested for 10,000 hours is statistically equal to 10 units tested for 1000 hours each and 50 units tested for 200 hours each.

Example 13.2

We want to test some power supplies to prove an MTBF goal of 50,000 hours of operation. How many units do we test and for how long, assuming one failure?

$$(\text{Sample size})(\text{test time}) = \text{MTBF goal}\left(X^2_{\alpha;2}\right)/2$$

In this case, using the 90% confidence level, $\alpha = 0.10$ and $r = 2(1) + 2$ or 4. Looking at the χ^2 chart in Appendix 1, go across the top row of the chart and find 0.10. Go down that column to the line for $v = 4$. There you will find the number 7.779. Put this into the equation:

$$\begin{aligned}(\text{Sample size})(\text{test time}) &= \text{MTBF goal}\,(7.779)/2\\ (\text{Sample size})(\text{test time}) &= 50{,}000\,(7.779)/2\\ &= 194{,}475\ \text{unit-hours}\end{aligned}$$

TABLE 13.3
Test Time Possibilities from Example 13.1

Sample Size	Test Time (Hours)
3	38,417
5	23,050
10	11,525
15	7683
20	5763
25	4610
50	2305
100	1153

TABLE 13.4
Test Possibilities from Example 13.2

Sample Size	Test Time (Hours)
3	64,825
5	38,895
10	19,448
15	12,965
20	9724
25	7779
50	3890
100	1945

From these data, we can calculate the possibilities listed in Table 13.4. Again, these data are based on the statistical law that states that 1 unit tested for 10,000 hours is statistically equal to 10 units tested for 1000 hours each and 50 units tested for 200 hours each.

An interesting observation is that one failure increased the test time by 69%. A second failure would yield the following equation:

$$\begin{aligned}(\text{Sample size})(\text{test time}) &= 50,000\,(10.645)/2\\ &= 266,125\end{aligned}$$

This is an increase in time of 37% over the one-failure example and 131% over zero failures. This proves that unreliability is costly in time and effort.

13.8 TYPES OF TESTING

13.8.1 Verification

This refers to procedures that attempt to determine that the product of each phase of the development process is an implementation of a previous phase, that is, it satisfies it. Each verification

activity is a phase of the testing life cycle. The testing objective in each verification activity is to detect as many errors as possible. The testing team should leverage its efforts by participating in any inspections and walk-throughs conducted by development and by initiating verification, especially at the early stages of development.

13.8.2 Validation

Validation is the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements.

13.8.3 Black Box

The easiest way to understand black box testing is to visualize a black box with a set of inputs coming into it and a set of outputs coming out of it. The black box test is performed without any knowledge of the internal structure. The black box test verifies that the end-user requirements are met from the end user's point of view.

Black box testing is a data-driven testing scheme. The tester views the device or program as a black box, that is, the tester is not concerned about the internal behavior and structure. The tester is only interested in finding circumstances in which the device or program does not behave according to its specification. Black box testing that is used to detect errors leads to exhaustive input testing, as every possible input condition is a test case.

13.8.4 White Box

White box testing is the opposite of black box testing. It is performed by personnel who are knowledgeable of the internal structure of the device and are testing from the developer's point of view. White box testing is a logic-driven testing scheme. The tester examines the internal structure of the device or program and derives test data from an examination of the internal structure. White box testing is concerned with the degree to which test cases exercise or cover the structure of the device or program. The ultimate while box test is an exhaustive path test.

13.8.5 Hardware Testing

Hardware testing includes various types of tests depending on the intended use of the device. Testing that occurs during almost every product development cycle includes the following:

- Vendor evaluation
- Component variation
- Environmental testing
- Safety evaluation
- Shipping tests
- Standards evaluation
- Product use/misuse
- Reliability demonstration

Often, hardware testing, especially that associated with the calculation of reliability parameters, is performed twice during the development process. The first occurs immediately after the design phase and evaluates the robustness and reliability of the design. The second occurs after production of customer units begins. This testing evaluates the robustness and reliability of the manufacturing process.

13.8.6 Software Testing

Software testing consists of several levels of evaluation. Initially, module testing occurs, where the individual modules of the software program are evaluated and stress-tested. This testing consists of verifying the design and implementation of the specification at the smallest component of the program. Testing involves running each module independently to assure it works and then inserting errors, possibly through the use of an emulator. The test is basically an interface between the programmer and the software environment.

Integration testing occurs after each of the modules has been successfully tested. The various modules are then integrated with each other and tested to assure they work together.

System testing consists of merging the software with the hardware to assure that both will work as a system. Testing involves verifying the external software interfaces; assuring that the system requirements are met; and assuring that the system, as a whole, is operational.

Acceptance testing is the final review of all the requirements specified for the system and assuring that both hardware and software address them.

13.8.7 Functional Testing

Functional testing (Table 13.5) is designed to verify that all the functional requirements have been satisfied. This type of testing verifies that given all the expected inputs, all of the expected outputs are produced. This type of testing is termed *success-oriented testing* because the tests are expected to produce successful results.

Testing of the functional capabilities involves the exercising of the operational modes and the events that allow a transition between the various software operational states. These tests are performed to verify that proper mode transitions are executed and proper outputs are generated given the correct inputs. These tests also verify that the software generates the expected output given the expected user input. A communication test tool should be utilized to test the proper operation of the remote communications protocol and functionality of the communications software located in the product under test. Timing tests should be performed for system critical functions relating to the system critical time and the operational window. Battery tests should be performed whenever a software change to the software that monitors the battery levels has been made. In addition, if new

TABLE 13.5
Examples of Functional Testing

Test Type	Example
Functional modes	Transitions between operational modes
	Correct inputs generate correct outputs
	Inputs and outputs include switches, tones, messages, and alarms
Remote communications	Connect and disconnect tests
	Valid commands and inquiries tests
	Handling of invalid commands and inquiries
	Tests for all baud rates supported
	Corrupted frames tests
	Error handling in general and the interface to the error handler
	Control mode testing with emphasis on safety
	Monitor mode testing with emphasis on fidelity of values reported
Timing	Active failure tests are completed within the system critical time
	Passive failure tests are completed within the operational window
Battery	Ramp-up and ramp-down of voltages
	Test the various levels of warnings, alarms, and errors

TABLE 13.6
Examples of Robustness Testing

Test Type	Example
Boundary	Over and under specified limits
	Numerical values that determine logic flow based on a maximum or minimum value
	Negative numerical values
Overflow and underflow	Values too large for all algorithms
	Values too small for all algorithms
User interface	Enter unexpected values
	Enter unexpected sequences
Execution time line processing	Routines that have execution time limits are altered to introduce delays
	Tasks that have execution time limits are altered to introduce delays
	Routines with execution constraints due to parametric calculations are altered
Data transmission	Unexpected commands are transmitted to the remote communications handler
	Unexpected data are transmitted to the remote communications handler

functionality is pushing the product to the absolute performance edge, then battery tests should also be performed because of its potential effect on any power-down software routines.

13.8.8 Robustness Testing

Robustness testing (Table 13.6) is designed to determine how the software performs given unexpected inputs. Robustness testing determines whether the software recovers from an unexpected input, locks the system in an indeterminate state, or continues to operate in a manner that is unpredictable. This type of testing is termed *failure oriented* because the test inputs are designed to cause the product to fail given foreseeable and reasonably unforeseeable misuse of the product.

Robustness testing is performed in order to determine software responses at the boundary limits of the product or test and manufacturing equipment, and the test cases should include negative values.

As a part of robustness testing, algorithms are tested for overflow and underflow. The user interface is tested by entering unexpected values and sequences. Routines, tasks, or processes that are time constrained are altered to introduce reasonable delays in order to determine the reaction of the product or equipment. Communication software is given unexpected commands and data that are then transmitted to the remote communications handler.

13.8.9 Stress Testing

Stress testing (Table 13.7) is designed to ascertain how the product reacts to a condition in which the amount or rate of data exceeds the amount or rate expected. Stress tests can help determine the margin of safety that exists in the product or equipment.

Stress tests are performed that exercise the equipment continuously over varying periods of time and operating parameters if latent errors exist in the software. Generally, these tests consist of overnight runs and weekend runs that gain the optimum benefit of the allotted test time. Global buffers and data structures are tested under loaded and overflow conditions in order to determine the response of the software. Remote communications load tests should be performed that verify the remote communications interface transfer rate at the maximum transfer rate under worst-case and maximum-load conditions. Worst-case-scenario tests verify the product or equipment operating capability under the projected worst-case scenario. The worst-case scenario for products generally includes highest execution rate and event overload for event-driven systems. These tests should be limited to reasonable environmental tests, which do not include temperature and vibration testing.

TABLE 13.7
Examples of Stress Testing

Test Type	Example
Duration	Overnight runs
	Weekend runs
	Others types of software burn-in tests
Buffer overload	Global buffers tested under loaded and overflow conditions
	Global data structures tested under loaded and overflow conditions
Remote communications	Verify the transfer at the maximum transfer rate
	Verify the transfer at the maximum transfer rate under maximum load conditions
Worst-case scenario	Verify the product and test and manufacturing equipment operating capability under projected worst case
	Highest execution rate
	Event overload for event-driven system

13.8.10 Safety Testing

Safety testing (Table 13.8) is designed to verify that the product performs in a safe manner and that a complete assessment of the safety design has been accomplished.

Fail-safe tests should be performed specifically to verify the fail-safe provisions of the software design. These tests cover the error conditions only and do not address warnings or alarms, which are more appropriately tested under the functional tests. Limited, nondestructive fault insertion tests should be performed by the software verification and validation engineers. Products require an analysis of the error-handling routines as well as data corruption tests to ensure an acceptable level of safety. The analysis must include a review of the products active failure tests so that they are completed within the system critical time and within the product-defined operational window. A number of safety aspects that must also be addressed are the protection of critical parameters and events that lead to a loss of safety critical indicators. Safety testing of the product must utilize the hazards analysis in relation to failures. In addition, validation safety tests and internal product safety self-tests that were performed on past products should be compiled, executed, and compared against the new product under test in order to arrive at a consistent and growing list of mandatory safety tests.

13.8.11 Regression Testing

Regression testing (Table 13.9) is performed whenever a software change or a hardware change that affects the software has occurred. Regression testing verifies that the change produces the desired effect on the altered component and that no other component that relies on the altered component is adversely affected.

Regression testing is performed on products and test and manufacturing equipment that have made a change to an established, validated baseline. Regression testing begins by comparing the new software to the existing baseline with a version difference tool and the generation of a cross-reference listing to assess the changes and to ensure that no unintended side effects are introduced. From this, an assessment of the amount of changes and their criticality is made, the level of effort that is required to perform the regression is estimated, and the risk is assessed. The alterations are tested and a compiled list of core tests executed in order to establish that no new unintended changes have been introduced. Special attention must be made to the safety implications.

TABLE 13.8
Examples of Safety Testing

Test Type	Example
Fail-safe	Verify that fail-safe provisions of the software design
	Test error conditions and handling
	Test data corruption
Active failure	Test completion within system critical time
	Read only memory (ROM) testing via cyclic redundancy check (CRC) computation and comparison to a stored value
	Random access memory (RAM) testing for stuck bits in data and address paths
	RAM testing for address decoding problems
	Light emitting diode (LED) indicator voltage tests
	Processor and controller tests
Passive failure	Watchdog timer test
	Watchdog disable tests
	Hardware RAM tests
	CRC generator
	Battery test
	Audio generator and speaker tests
	Electrically erasable programmable read only memory (EEPROM) tests
Safety	Critical parameters and their duplicates
	Events that lead to a loss of audio indicators
	Events that lead to a loss of visual indicators
	Events that lead to tactile errors, such as a key press
	Error handling for corrupted vectors and structures
	Error handling for corrupted sanity checks
	Sufficiency of periodic versus aperiodic tests
From hazard analysis	Single point failures
	Normal power-up, run-time, and power-down safety tests

TABLE 13.9
Regression Testing Sequence

Sequence Step	Activity
1	Compare the new software to the existing baseline
2	Generate a cross-reference listing to assess changes and to ensure no unintended side effects
3	Assess the amount of changes and the criticality
4	Determine the level of effort required and assess the risk
5	Test the new functions and the debug fixes
6	Execute a predetermined set of core tests to confirm no new unintended changes
7	Devote special attention to the safety implications

13.9 HIGHLY ACCELERATED STRESS TESTING

The highly accelerated stress test (HAST) method was invented by Nihal Sinnadurai while working as a research engineer at British Telecommunications Research Laboratories in 1968 in order to perform highly accelerated reliability testing of electronics components that are likely to encounter humid environments during normal (ambient) operation. The method uses the principle of a nonsaturating autoclave designed and engineered with no moving parts, to deliver close temperature (<1°C)

and humidity (<2% RH) control and a high reliability of the stress equipment. Nihal Sinnadurai and his team carried out many millions of device hours of reliability stress testing in HAST chambers and arrived at a clear correlation with a humidity exponent as the stress-accelerating agent. The generic Sinnadurai–HAST (SH) model he developed by analyzing the experimentally determined data is

$$t_{amb}/t_s = e^{X\left[(RH_s)^n-(RH_{amb})^n\right]+(EA/k)(1/T_{amb}-1/T_s)}.$$

When applied to semiconductor devices, the empirical SH model expression is

$$t_s = 175{,}000/e^{0.00044\left[(RH_s)^2-(RH_{amb})^2\right]+7000(1/T_{amb}-1/T_s)}.$$

When applied to thick-film elements, the empirical SH model is

$$t_s = 175{,}000/e^{0.025\left[(RH_s)-(RH_{amb})\right]+8120(1/T_{amb}-1/T_s)},$$

where 175,000 is approximately 20 years and is the required lifetime (t_{amb}) at the ambient condition, RH_s is the applied humidity stress, RH_{amb} is the humidity at the application ambient, T_s is the applied stress absolute temperature, and T_{amb} is the application ambient temperature.

HAST was developed as a shorter alternative to temperature humidity bias (THB) testing. If THB testing takes 1000 hours to complete, HAST results are available within 96–100 hours. Because of this, the popularity of HAST has continuously increased in recent years, to the extent that some companies have totally replaced THB testing with HAST.

Like THB testing, HAST accelerates corrosion, particularly that of the die metal lines and thin-film resistors. HAST requires preconditioning and is conducted with electrical bias at 130°C and 85% RH for 96–100 hours.

Electrical bias during HAST stressing must be defined based on the following guidelines:

1. Power dissipation must be minimized to ensure that moisture is always present at the die surface.
2. Alternate pins must be subjected to opposite bias (low voltage versus high voltage) as much as possible.
3. Potential differences between the various metallizations on the die must be maximized.
4. The operating voltage range for the device must also be maximized, as long as the power dissipation is kept under control.

The samples for HAST stressing are loaded into HAST boards prior to loading into the HAST chamber. HAST boards are designed to withstand the severe test conditions of HAST and are, therefore, relatively expensive. The HAST boards are then inserted into board racks inside the chamber of the HAST system.

13.10 HIGHLY ACCELERATED LIFE TESTING

A highly accelerated life test (HALT) is a stress-testing methodology for accelerating product reliability during the engineering development process. It is commonly applied to electronic equipment and is performed to identify and thus help resolve design weaknesses in newly developed equipment. Thus it greatly reduces the probability of in-service failures (i.e., it increases the product's reliability). Progressively more severe environmental stresses are applied building to a level significantly beyond what the equipment will see in service. By this method, weaknesses can be identified

using a small number of samples (sometimes one or two but preferably at least five) in the shortest possible time and at least expense.

A second function of HALT testing is that it characterizes the equipment under test and identifies the equipment's safe operating limits and design margins. Data from a HALT test is therefore used as a basis for the design of an optimal highly accelerated stress screening (HASS) test, which is used to screen every piece of production equipment for latent manufacturing defects and defective components. HASS is an extension of HALT but is applied during production.

Individual components, populated printed circuit boards, and whole electronic systems can be subjected to HALT testing. The size of the test sample is governed by many factors including the number of samples available, cost, type of stresses applied, and physical size. For example, component manufacturers can typically test thousands of individual components at one time, whereas often, it is not economically feasible to write off more than a few items of very expensive equipment because production quantities or the application does not justify the cost. A general principal is that while a HALT test can and should be conducted at unit level, it is very desirable to conduct it at subassembly and piece-part level as well.

Temperature cycling and random vibration, power margining, and power cycling are the most common form of failure acceleration for electronic equipment. HALT does not measure or determine equipment reliability, but it does serve to improve the reliability of a product. It is an empirical method used across industry to identify the limiting failure modes of a product and the stresses at which these failures occur.

A significant advantage of accelerated life testing is that it can be conducted during the development phase of a product to weed out design problems and marginal components. Thus, a consumer products company can achieve better customer satisfaction because fewer products have to be returned for repair, and can also save money on warranty returns, or an aerospace manufacturer can avoid catastrophic failures in aircraft or space vehicles. Another major advantage is that the design team can be moved on to designing new products rather than becoming occupied with problems in older products.

On military design and development programs, HALT is conducted before qualification testing. By so doing, significant cost savings can be accrued, because the formal qualification of the equipment and subsequent customer acceptance will proceed more rapidly and at lower cost, and the need for multiple redesigns and repeat testing (regression tests) will be greatly reduced or eliminated.

Several standards and test methods are available for a HALT test. Different stresses are applied with different failures occurring during each. The types of stress typically employed are as follows:

- Cold step
- Hot step
- Rapid temperature cycling
- Stepped vibration (random)
- Combined environment stress (temperature cycling and random vibration plus power switching and power margining, defined as a means of verifying the robustness of a product by intentionally adjusting its supply voltages to their limits and then valuating the product's performance to ensure that it still meets its specifications at the power supply's extremes)

In HALT, these stresses are applied in a controlled, incremental fashion while the unit under test is continuously monitored for failures. Once the weaknesses of the product are uncovered and corrective actions taken, the limits of the product are clearly understood, and the operating margins have been extended as far as possible. The result is that a much more mature product can be introduced much more quickly with a higher degree of reliability.

When HALT testing is applied during the design process, it can produce a very robust product without undue cost, because improvements are targeted only where they are needed. As failure

modes are discovered and understood, the product life can increase significantly. This makes the product more robust, and risk of failure reduces drastically.

Individual components such as resistors, capacitors, and diodes; printed circuit boards; and whole electronic products such as cell phones, PDAs, and televisions eventually fail at different rates under different end-user stress levels. For example, a typical consumer-owned television will not likely be operated at temperatures outside the range of normal living accommodations or subjected to mechanical stress by being repeatedly dropped. A cell phone, on the other hand, may be dropped from 3 or 4 feet off the ground fairly often and subjected to a varying range of vibrations. A commercial telephone switch may be required to operate in remote installations ranging from Barrow, Alaska, to Phoenix, Arizona, at an ambient temperature range of from −50°F to +120°F. Components used in military and aerospace applications may be subjected to even more severe operating temperature requirements as well as high g-forces and ionizing radiation, sometimes simultaneously, to meet specific Military Specification (MIL-SPEC) standards.

Therefore, failure-rate data used to select any device in a product must correlate with the stress levels in the product or application. To accomplish this, the required lifetime and operating conditions for the product into which the components are designed must first be determined. For instance, in the previous examples, the television set may only be required to operate through its warranty period, whereas the telephone switch may be required to operate without being serviced for 10 years or more. Components used in a missile may only be required to operate for a few hours of testing and a few minutes of actual use, but their failure rate will be expected to be zero during that period. Devices used in satellites or space vehicles where replacement is not possible are expected to have a zero failure rate for the lifetime of the vehicle. Knowing the required failure rate as determined by the application, components can be selected based on the failure-rate data supplied by the manufacturer as described prior.

Typically, components used in consumer devices are chosen by finding the least expensive component that will meet the requirement for the warranty period. At the other end of the scale, components used in aerospace applications are more likely to be chosen for maximum reliability independent of cost. Moreover, due to cost, warranty failures are usually not expected to be zero during the warranty period but, rather, are expected to not exceed a level that might subject the manufacturer to unwanted publicity or legal action. Additionally, the failure rate for critical components may be required to be lower than for other components in a system. For instance, components in an automobile that may cause so-called "walk-home failures" are usually subject to higher reliability requirements than are components in the automobile's entertainment or security systems.

Once the product or device is deployed or sold into the marketplace, proper quality control procedure requires that the "quality loop" be closed by retrieving all components that fail in the field during the predicted lifetime, analyzing them to determine why they failed before they were predicted to fail, and determining where the reliability failure prediction was in error. Information from these analyses should then be used for appropriate corrective action in the reliability failure prediction methods.

13.11 OTHER ACCELERATED TESTING

The length of time available to conduct a test determines whether the test is performed in a standard or an accelerated mode. In the standard mode, tests are run at ambient temperature and typical usage parameters. The test time is the actual time of operation. In the accelerated mode, test time is reduced by varying parameters, such as temperature, voltage, or frequency of cycling, above their normal levels or by performing a test, such as sudden-death testing.

Accelerated testing is a shortening of the length of the test time by varying the parameters of the test. Testing can be accelerated in several ways:

- Increase the sample size
- Increase the test severity

13.11.1 Increased Sample Size

Reliability tests are accelerated by increasing the sample size, provided the life distribution does not show a wear-out characteristic during the anticipated life. Test time is inversely proportional to the sample size, so that increasing the sample size reduces the test time.

A large-sample-size reliability test conducted to provide a high total operating time should be supported by some long-duration tests if there is a reason to suspect that failure modes exist that have high times to failure.

13.11.2 Increased Test Severity

Increasing test severity is a logical approach to reducing test time when large sample sizes cannot be used.

The severity of tests may be increased by increasing the stresses acting on the test unit. These stresses can be grouped into two categories:

- Operational, such as temperature and humidity
- Application, such as voltage, current, self-generated heat, or self-generated mechanical stresses

Increasing the temperature severity is the usual method of accelerating testing.

It is important, in accelerated testing, to ensure that unrealistic failure modes are not introduced by the higher stresses. It is also possible that interactions may occur between separate stresses, so that the combined weakening effect is greater than would be expected from a single additive process.

When conducting accelerated testing, an essential calculation is acceleration factor, that is, the parameter that indicates how much acceleration was conducted. To calculate the acceleration factor, the following equation (Arrhenius model based) is used[1]:

$$\text{Acceleration factor} = \exp[-(EA/K)(1/TA - 1/TU)]$$

where

EA = energy of activation (0.5 eV)
K = Boltzmann's constant (0.0000863 eV/Kelvin)
TU = use temperature in Kelvin
TA = accelerate temperature in Kelvin

Example 13.3

Ten power supplies are tested to failure at 150°C. The units are expected to be used at 85°C. What is the minimum life (time of the first failure) at 85°C? What is the MTBF at 85°C?

The failure rates in hours are listed as

2750	3100	3400	3800	4100
4400	4700	5100	5700	6400

Calculation of acceleration factor:

AE = 0.5
K = 0.0000863
TU = 85 + 273 = 358 Kelvin
TA = 150 + 273 = 423 Kelvin

$$\begin{aligned}\text{Acceleration factor} &= \exp[-(EA/K)(1/TA - 1/TU)] \\ &= e[-(0.5/0.0000863)(1/423 - 1/358)] \\ &= 12\end{aligned}$$

Calculation of minimum life at 85°C:

$$\begin{aligned}\text{Minimum life} &= \text{acceleration factor} \times \text{failure at } 85°C \\ &= 12 \times 2750 \\ &= 33{,}000 \text{ hours}\end{aligned}$$

Calculation of MTBF at 150°C:

$$\begin{aligned}\text{MTBF} &= \text{sum of the times of operation/number of errors} \\ &= 2750 + 3100 + 3400 + 3800 + 4100 + 4400 \\ &\quad + 4700 + 5100 + 5700 + 6400/10 \\ &= 43{,}450/10 \\ &= 4345 \text{ hours}\end{aligned}$$

Calculation of MTBF at 85°C:

$$\begin{aligned}\text{MTBF} &= \text{acceleration factor (MTBF at } 150°C) \\ &= 12(4345) \\ &= 52{,}140 \text{ hours}\end{aligned}$$

Example 13.4

Integrated circuits are to be burned in to eliminate infant mortality failures. We want the burn-in to be equivalent to 1000 hours of operation at ambient temperature (24°C). How long do we run the units at 50°C? How long do we run the units at 100°C?

Calculation at 50°C:

$$\begin{aligned}\text{Acceleration factor} &= \exp[-(EA/K)(1/TA - 1/TU)] \\ &= e[(0.5/0.0000863)(1/323 - 1/297)] \\ &= 4.8\end{aligned}$$

$$\begin{aligned}\text{Length of run time} &= \text{run time at } 24°C/\text{acceleration factor} \\ &= 1000/4.8 \\ &= 208 \text{ hours}\end{aligned}$$

Calculation at 100°C:

$$\text{Acceleration factor} = e[(0.5/0.0000863)(1/297 - 1/373)]$$
$$= 53$$

$$\text{Length of time} = 1000/53$$
$$= 19 \text{ hours}$$

EXERCISES

1. You have the responsibility for writing the test protocol for a portable pulse oximeter that will be used in a high school science class. Detail a list of tests that you would use.
2. You must determine why your blood sugar determination kit, which worked so well when tested in Nashville, TN, gives erroneous results when used in Salt Lake City. What did you not account for?
3. What common fluid spills would you plan for in testing an EKG monitor in use in an operating room? How would this list differ for the same machine in the patient's room?
4. The lobby and part of the immediate exterior of the Vanderbilt University Hospital has a floor made of mortared bricks. On the inside, they are shellacked; on the outside, they are allowed to weather. What tests can be performed with this flooring?
5. While occupied, an electric wheelchair moved of its own accord in a hospital environment, injuring the occupant. How would you investigate this accident? What tests were probably not run properly on the wheelchair prior to sale?
6. You are placed in charge of specifying shipping containers for a computer-based medical device. Investigate how the ISTA can assist you in specification of tests and shipping containers. (Visit the website for this organization at http://www.ista.org.)
7. You are in charge of setting up the test sequence for a new heart bypass pump system. The system has a C++ software control scheme for flow control. Maximum expected length of use of the machine will be for surgeries lasting no more than 6 hours. List some of the test methods you would use for this device.
8. Estimate the types of test necessary for validation of an implanted defibrillator system. What would the minimum number of tests be determined by?
9. Purely mechanical systems need not undergo some of the tests that software/hardware systems do. Contrast the types of tests you would perform on an artificial knee versus the types of tests you would perform on an insulin pump.

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14 Analysis of Test Data

> Testing leads to failure, and failure leads to understanding.
>
> **Burt Rutan**

The heart of reliability is the analysis of data, from which desired reliability parameters can be calculated. These parameters are calculated from testing throughout the product development process. Early calculations are updated as the program progresses and the presence or lack of reliability improvement becomes apparent.

Reliability parameter calculation assumes that the product is in the useful life period of the normal life cycle of device failures versus time ("bathtub curve"). During this period, the failure rate is constant, and the exponential distribution (normal Gaussian) is used for calculations. In standards and handbooks where failure rates and mean time between failures (MTBF) values are listed, the same assumption is made, and the exponential distribution is used.

Calculations of some parameters, such as MTBF, are dependent upon the termination mode of the test. Time-terminated tests, where tests are ended after a predetermined time period has elapsed, are calculated differently than failure-terminated tests, where tests are ended after a predetermined number of units have failed.

The calculations necessary to determine the following parameters will be reviewed:

- Failure rate
- MTBF
- Reliability
- Confidence limits

In addition, graphical analysis and its application to dealing with reliability data will be discussed.

14.1 THE DEFINITION OF RELIABILITY

The idea of quality over a period of time is reflected in the more formal definition of reliability:

> The probability, at a desired confidence level, that a device will perform a required function, without failure, under stated conditions, for a specified period of time.

This definition contains four key requirements:

To perform a required function, the function must have been established through such activities as customer and/or market surveys, establishing requirements, and documenting and tracing the requirements. Thus, reliability requires the device to be fully specified prior to design.

To perform without failure, the normal operation of the device must be defined, in order to establish what a failure is. This activity also includes anticipating the misuse to which the device could be subjected and designing around it.

To perform under stated conditions, the environment in which the device will operate must be specified. This includes typical temperature and humidity ranges, shock and vibration, the shipping environment, and interference from associated equipment or to other equipment experienced in normal usage.

To operate for a specified period of time, the life expectancy of the device must be defined as well as typical daily usage.

In summary, reliability assumes that preliminary thought processes have been completed and that the device and its environment have been completely defined. These criteria make the task of the designer easier and less costly in time and effort. It assumes that failure-free or failure-tolerant design principles are used. It assumes that manufacturing processes are designed so that they will not reduce the reliability of the device.

The user of a medical device does not need such a formal definition. From the customer point of view, a reliable product is as follows:

One that does what the customer wants to do,
when the customer wants to do it.

Anything else is unreliable and totally unacceptable.

Reliability, like any science, depends upon other technical areas as a base for its functionality, including the following:

- Basic mathematics and statistics
- Current regulatory standards
- Design principles
- Software quality assurance
- System interface principles
- Human factors
- Cost/benefit analysis
- Common sense

14.2 TYPES OF RELIABILITY

Reliability is composed of four primary subdivisions, each with its own particular attributes:

- Electronic reliability
- Mechanical reliability
- Software reliability
- System reliability

14.2.1 Electronic Reliability

Electronic reliability (Figure 14.1) is a function of the age of a component or assembly. The failure rate is defined in terms of the number of malfunctions occurring during a period of time. As is evident from the figure, the graph is divided into three distinct time periods:

- Infant mortality
- Useful life
- Wear-out

14.2.1.1 Infant Mortality

Infant mortality is the beginning of the life of an electronic component or assembly. This period is characterized by an initial high failure rate, which decreases rapidly and then stabilizes. These failures are caused by gross, built-in flaws due to faulty workmanship, bad processes, manufacturing

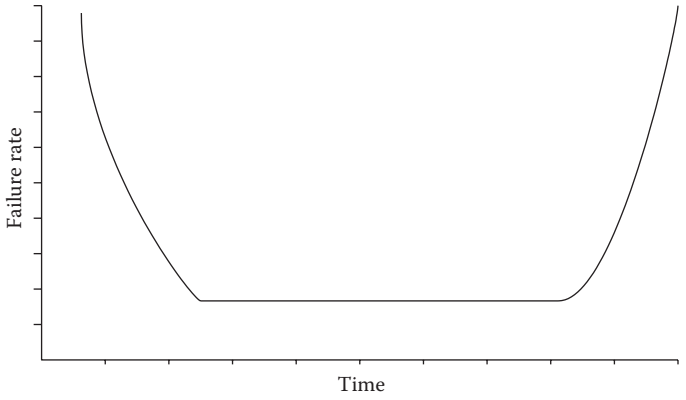

FIGURE 14.1 Electronic reliability curve.

deviations from the design intent, or transportation damage. Examples of early failures include the following:

- Poor welds or seals
- Poor solder joints
- Contamination on surfaces or in materials
- Voids, cracks, or thin spots on insulation or protective coatings

Many of these failures can be prevented by improving the control over the manufacturing process or by screening components. Improvements in design or materials are necessary for these manufacturing deviations. A "burn-in" time may be mandated at the manufacturing end point and may be required to screen out these early failures to keep these units from shipping. (In the early days of personal computer manufacture, units were typically turned on for a minimum of 24 hours; units still working at that end point were deemed shippable.)

14.2.1.2 Useful Life

The useful life period of a component or assembly is the largest segment of the life cycle and is characterized by a constant failure rate (the midsection of Figure 14.1). During this period, the failure rate reaches its lowest level and remains relatively constant. Failures occurring during this period either are stress related or occur by chance. Chance failures are the most difficult failures to repeat or analyze.

14.2.1.3 Wear-Out

The final period in the life cycle occurs when the failure rate begins to increase rapidly. Wear-out failures are due primarily to deterioration of the design strength of the components or assemblies, as a consequence of operation and/or exposure to environmental influences. Such deterioration may result from the following:

- Corrosion or oxidation
- Insulation breakdown or leakage
- Ionic migration of metals on surfaces
- Shrinkage and cracking in plastics

Replacing components prior to reaching the wear-out period through a preventive maintenance program can prevent wear-out failures and increase the reliability of the product.

14.2.2 Mechanical Reliability

Mechanical reliability (Figure 14.2) differs considerably from electronic reliability in its reaction to the aging of a component or assembly. Mechanical components or assemblies typically begin their life cycle at a failure rate of zero and experience a rapidly increasing failure rate. This curve approximates the wear-out portion of the electronics life curve.

Mechanical failures are due primarily to deterioration of the design strength of the component or assembly. Such deterioration may result from the following:

- Frictional wear
- Shrinkage and/or cracking in plastics
- Fatigue
- Surface erosion
- Corrosion
- Creep
- Material strength deterioration

Optimization of mechanical reliability occurs with timely replacement of components and/or assemblies through preventive maintenance, before the failure rate reaches unacceptably high levels.

14.2.3 Software Reliability

Assurance that a product works reliably has been classically provided by a test of the product at the end of its development cycle. However, because of the nature of software, no test appears sufficiently comprehensive to adequately test all aspects of a program. Software reliability has developed to include directing and documenting the development process itself, including checks and balances.

The following definition of reliability is given by the *IEEE Standard Glossary of Software Engineering Terminology*:

> The ability of a system or component to perform its required functions under stated conditions for a specified period of time.

In the case of medical device software, that definition should be expanded to include the concepts of safety and efficacy as follows:

> The ability of a system or component to perform its required functions in a safe and effective manner, under stated conditions, for a specified period of time.

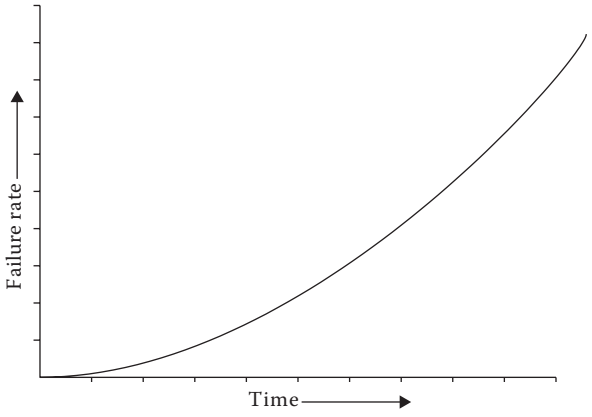

FIGURE 14.2 Mechanical reliability curve.

In order to apply this definition, the software developer must know exactly what the "required functions" of the particular medical device are. Sometimes, such functional definitions are obvious, but in general, they are not. Such knowledge requires the existence of a formal software specification. In addition, the software developer must know the "stated conditions." This means that the environment in which the software is to operate must be fully defined. This may include whether the software will be operated during a stressful situation, the lighting and noise levels in the area of operation, and the technical knowledge of the user. "For a specified period of time" indicates that the reliability is being measured for a specific period of time, known as a mission time. This may be the length of a surgical case, the warranty period for the device, or the total operational life of the device. The main point of this definition is that reliability, safety, and efficacy are inseparable requirements for medical device software.

A more practical definition of software reliability is the planned and systematic pattern of activities performed to assure that the procedures, tools, and techniques used during software development and modification are adequate to provide the desired level of confidence in the final product. The purpose of the software reliability program is to assure that the software is of such quality that it does not reduce the reliability of the device.

Software reliability differs considerably from both electronic and mechanical reliability in that software is not subject to the physical constraints of electronic and mechanical components. Software reliability consists of the process of preventing failures through structured design and detecting and removing errors in the coding. Once all "bugs" are removed, the program will operate without failure forever (Figure 14.3). However, practically, the software reliability curve may be as shown in Figure 14.4, with early failures as the software is first used and a long period of constant failures, as bugs are fixed.

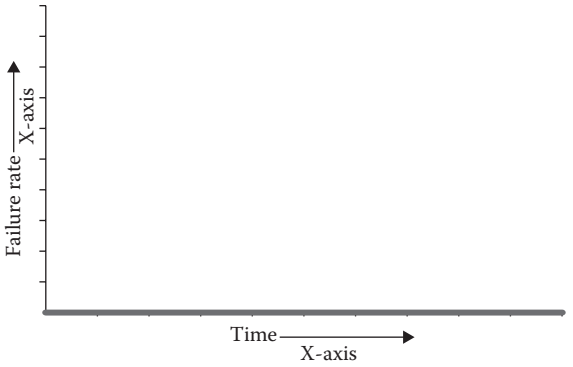

FIGURE 14.3 Ideal software reliability curve.

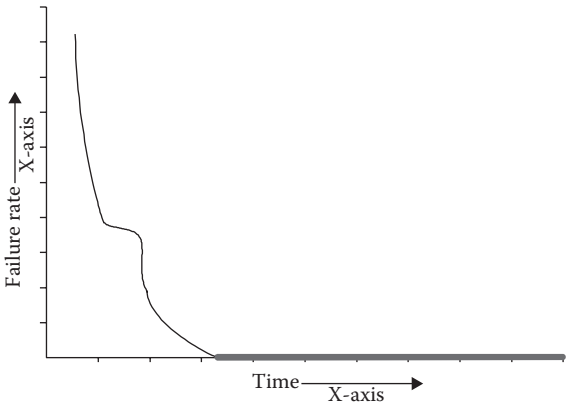

FIGURE 14.4 Practical software reliability curve.

Software failures are due primarily to the following:

- Specification errors (40%–50%)
- Design errors
- Coding errors
- Resource errors
- Time-critical errors

These are discussed in detail in Chapter 2.

14.2.4 System Reliability

The life cycle of any medical device may be represented by a graph known as the reliability bathtub curve (Figure 14.5). It is a graph of failure rate versus the age of the device. The graph is identical to that for electronics described above. As with the electronics life curve, there are three distinct time periods:

- Infant mortality
- Useful life
- Wear-out

The discussion of the three life periods contained in the section on electronic reliability applies to device reliability as well.

It must be remembered that most devices are composed of three functions (Figure 14.6):

- Hardware
- Software
- The human interface

When conducting device reliability measurements, reliability programs must include hardware reliability, software reliability, and optimization of human interaction with the device.

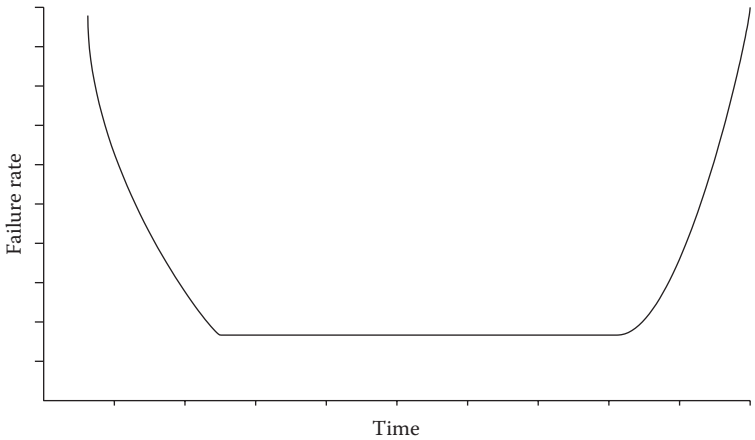

FIGURE 14.5 System reliability curve.

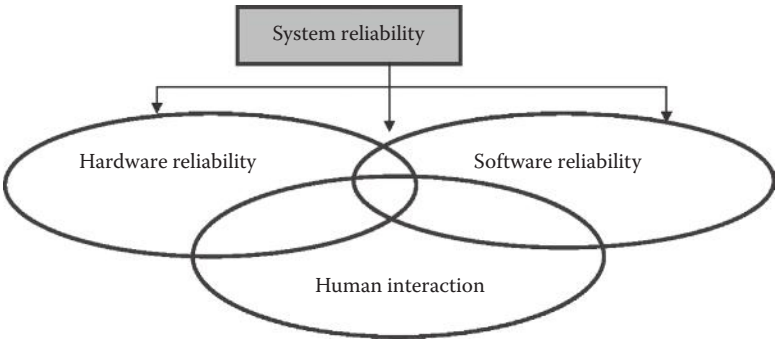

FIGURE 14.6 Device functions.

14.3 FAILURE RATE

Failure rate is the number of failures per million hours of operation. For devices in their useful life period, the failure rate is the reciprocal of the MTBF.

$$\text{MTBF} = 1/\lambda \tag{14.1}$$

The failure rate is stated as failures per hour for this equation.

Example 14.1

An electroencephalogram (EEG) machine has a MTBF of 4380 hours. What is the failure rate?

$$\begin{aligned}\lambda &= 1/\text{MTBF}\\ &= 1/4380\\ &= 0.000228 \text{ failures per hour}\\ &= 228 \text{ failures per million hours}\end{aligned}$$

Example 14.2

10 power supplies are put on test, to be terminated after each has completed 1000 hours of operation. Two power supplies fail, one at 420 hours and the other at 665 hours. What is the failure rate of the power supplies?

Eight units completed 1000 hours.

$$\begin{aligned}\text{Total test time} &= 8(1000) + 420 + 665\\ &= 9085 \text{ hours}\end{aligned}$$

$$\begin{aligned}\lambda &= \text{number of failures/total test time}\\ &= 2/9085\\ &= 0.000220 \text{ failures per hour}\\ &= 220 \text{ failures per million hours}\end{aligned}$$

14.4 MEAN TIME BETWEEN FAILURES

MTBF is the time at which 63% of the operational devices in the field will have failed. MTBF is the reciprocal of the failure rate. It is also calculated from test data dependent upon the type of test run, for example, time terminated or failure terminated, and upon whether the failed units were replaced or not. Five different methods of MTBF calculation are available:

- Time terminated, failed parts replaced
- Time terminated, no replacement
- Failure terminated, failed parts replaced
- Failure terminated, no replacement
- No failures observed during the test

14.4.1 Time Terminated, Failed Parts Replaced

$$\text{MTBF} = N(\text{td})/r \tag{14.2}$$

where

N = number of units tested
td = test duration
r = number of failures

Example 14.3

The performance of 10 pressure monitors is monitored while operating for a period of 1200 hours. The test results are listed below. Every failed unit is replaced immediately. What is the MTBF?

Unit Number	Time of Failure (Hours)
1	650
2	420
3	130 and 725
4	585
5	630 and 950
6	390
7	No failure
8	880
9	No failure
10	220 and 675

N = 10
r = 11
td = 1200 hours

$$\begin{aligned}\text{MTBF} &= N(\text{td})/r \\ &= 10(1200)/11 \\ &= 1091 \text{ hours}\end{aligned}$$

14.4.2 Time Terminated, No Replacement

$$\text{MTBF} = \left(\sum T_{\text{i}}\right) + (N - r)\text{td}/r$$

where
- N = number of units tested
- td = test duration
- r = number of failures
- T_{i} = individual failure times

Using the data in Example 14.3,

Unit Number	Time of Failure (Hours)
1	650
2	420
3	130
4	585
5	630
6	390
7	No failure
8	880
9	No failure
10	220

$$\begin{aligned}\text{MTBF} &= \left(\sum T_{\text{i}}\right) + (N - r)\text{td}/r \\ &= (650 + 420 + 130 + 585 + 630 + 390 + 880 + 220) \\ &\quad + 2(1200)/8 \\ &= (3905 + 2400)/8 \\ &= 788 \text{ hours}\end{aligned}$$

14.4.3 Failure Terminated, Failed Parts Replaced

$$\text{MTBF} = N(\text{td})/r$$

where
- N = number of units tested
- td = test duration
- r = number of failures

Example 14.4

Six transcutaneous nerve stimulator (TENS) units were placed on test until all units failed, the last occurring at 850 hours. The test results are listed below. Every failed unit, except the last one, is replaced immediately. What is the MTBF?

Unit Number	Time of Failure (Hours)
1	130
2	850
3	120 and 655
4	440
5	725
6	580

$$\begin{aligned}\text{MTBF} &= N(\text{td})/r \\ &= 6(850)/7 \\ &= 729 \text{ hours}\end{aligned}$$

14.4.4 Failure Terminated, No Replacement

$$\text{MTBF} = \left(\sum T_{\text{i}}\right) + (N - r)\text{td}/r$$

Using the data from Example 14.4

Unit Number	Time of Failure (Hours)
1	130
2	850
3	120
4	440
5	725
6	580

$$\begin{aligned}\text{MTBF} &= \left(\sum T_{\text{i}}\right) + (N - r)\text{td}/r \\ &= (130 + 850 + 120 + 440 + 725 + 580) + 0(850)/6 \\ &= 3945 + 0/6 \\ &= 658 \text{ hours}\end{aligned}$$

14.4.5 No Failures Observed

For the case where no failures are observed, an MTBF value cannot be calculated. A lower one-sided confidence limit must be calculated and the MTBF stated to be greater than that value.

$$m\text{l} = 2(T\text{a})/\chi^2_{\alpha;2}$$

where

*m*l = lower one-sided confidence limit
*T*a = total test time
$\chi^2_{\alpha;2}$ = the χ^2 value from the table in Appendix 1, where α is the risk level and 2 is the degrees of freedom

Example 14.5

10 ventilators are tested for 1000 hours without failure. What is the MTBF at a 90% confidence level?

N = 10
td = 1000
r = 0
1 − α = 0.90
α = 0.10
*T*a = *N*(td) = 10(1000) = 10,000

$$\begin{aligned} m\text{l} &= 2(T\text{a})/\chi^2_{\alpha;2} \\ &= 2(10{,}000)/\chi^2_{10;2} \\ &= 20{,}000/4.605 \\ &= 4343 \text{ hours} \end{aligned}$$

We can then state that the MTBF > 4343 hours, with 90% confidence.

14.5 RELIABILITY

Reliability has been defined as the probability that an item will perform a required function, under specified conditions, for a specified period of time, at a desired confidence level. Reliability may be calculated from either the failure rate or the MTBF. The resultant number is the percentage of units that will survive the specified time.

Reliability can vary between 0 (no reliability) and 1.0 (perfect reliability). The closer the value is to 1.0, the better the reliability will be. To calculate the parameter "reliability," two parameters are required:

- Either the failure rate or the MTBF
- The mission time or specified period of operation

$$\begin{aligned} \text{Reliability} &= \exp(-\lambda t) \\ &= \exp(-t/\text{MTBF}) \end{aligned}$$

Example 14.6

Using the data in Example 14.2, calculate the reliability of the power supplies for an operating period of 3200 hours.

λ = failure rate = 220 failures per million hours
For the equation, λ must be in failures per hour

Thus, 220/1,000,000 = 0.000220 failures per hour
t = 3200 hours

$$\begin{aligned}\text{Reliability} &= \exp(-\lambda t)\\ &= \exp-(0.000220)(3200)\\ &= \exp-(0.704)\\ &= 0.495\end{aligned}$$

This states that after 3200 hours of operation, one-half the power supplies in operation will not have failed.

Example 14.7

Using the time-terminated, no-replacement case, calculate the reliability of the pressure monitors for 500 hours of operation.

$$\begin{aligned}\text{Reliability} &= \exp-(\lambda t)\\ &= \exp-(t/\text{MTBF})\\ &= \exp-(500/788)\\ &= \exp-(0.635)\\ &= 0.530\end{aligned}$$

Thus, 53% of the pressure monitors will not fail during the 500 hours of operation.

14.6 CONFIDENCE LEVEL

Confidence level is the probability that a given statement is correct. Thus, when a 90% confidence level is used, the probability that the findings are valid for the device population is 90%.

Confidence level is designated as follows:

$$\text{Confidence level} = 1 - \alpha$$

where
α = risk level

Example 14.8

Test sample size is determined using a confidence level of 98%. What is the risk level?

$$\text{Confidence level} = 1 - \alpha$$

$$\begin{aligned}\alpha &= 1 - \text{confidence level}\\ &= 1 - 0.98\\ &= 0.02 \text{ or } 2\%\end{aligned}$$

14.7 CONFIDENCE LIMITS

Confidence limits are defined as the extremes of a confidence interval within which the unknown has a designated probability of being included. If the identical test was repeated several times with different samples of a device, it is probable that the MTBF value calculated from each test would not be identical. However, the various values would fall within a range of values about the true MTBF value. The two values that mark the end points of the range are the lower and upper confidence limits. Confidence limits are calculated based on whether the test was time or failure terminated.

14.7.1 Time-Terminated Confidence Limits

$$m\mathrm{L} = 2(T\mathrm{a})/\chi^2_{\alpha;2r+2}$$

where

mL = lower confidence limit
Ta = total test time
$\chi^2_{\alpha;2r+2} = \chi^2$ value from Appendix 1 for α risk level and $2r + 2$ degrees of freedom

$$m\mathrm{U} = 2(T\mathrm{a})/\chi^2_{1-\alpha/2;2r}$$

Example 14.9

Using the data from the time-terminated, no-replacement data from Example 14.3, at a 90% confidence limit:

Ta = 6305 hours
α = 1 − confidence level = 0.10
α/2 = 0.05
r = 8
$2r + 2$ = 18

$$\begin{aligned} m\mathrm{L} &= 2(6305)/\chi^2_{0.05;18} \\ &= 12610/28.869 \\ &= 437 \text{ hours} \end{aligned}$$

$$\begin{aligned} m\mathrm{U} &= 2(6305)/\chi^2_{0.95;16} \\ &= 12610/7.962 \\ &= 1584 \text{ hours} \end{aligned}$$

We can thus say:

$$437 < \mathrm{MTBF} < 1584 \text{ hours}$$

or the true MTBF lies between 437 and 1584 hours.

14.7.2 Failure-Terminated Confidence Limits

$$m\mathrm{L} = 2(T\mathrm{a})/\chi^2\alpha/2;2r$$

and

$$m\mathrm{U} = 2(T\mathrm{a})/\chi^2 1 - \alpha/2;2r$$

Using the data from the failure-terminated, no-replacement data from Example 14.4 at a 95% confidence limit:

Ta = 3945 hours
$\alpha = 0.05$
$\alpha/2 = 0.025$
$1 - \alpha/2 = 0.975$
$r = 6$
$2r = 12$

$$\begin{aligned} m\mathrm{L} &= 2(3945)/\chi^2_{0.025;12} \\ &= 7890/23.337 \\ &= 338 \text{ hours} \end{aligned}$$

$$\begin{aligned} m\mathrm{U} &= 2(3945)/\chi^2_{0.975;12} \\ &= 7890/4.404 \\ &= 1792 \text{ hours} \end{aligned}$$

Thus

$$338 < \mathrm{MTBF} < 1792$$

14.8 MINIMUM LIFE

The minimum life of a device is defined as the time of occurrence of the first failure.

14.9 GRAPHICAL ANALYSIS

Graphical analysis is a way of looking at test data or field information. It can show failure trends, determine when a manufacturing learning curve is nearly complete, indicate the severity of field problems, or determine the effect of a burn-in program.

Several types of graphical analysis are advantageous in reliability analysis:

- Pareto analysis
- Graphical plotting
- Weibull analysis

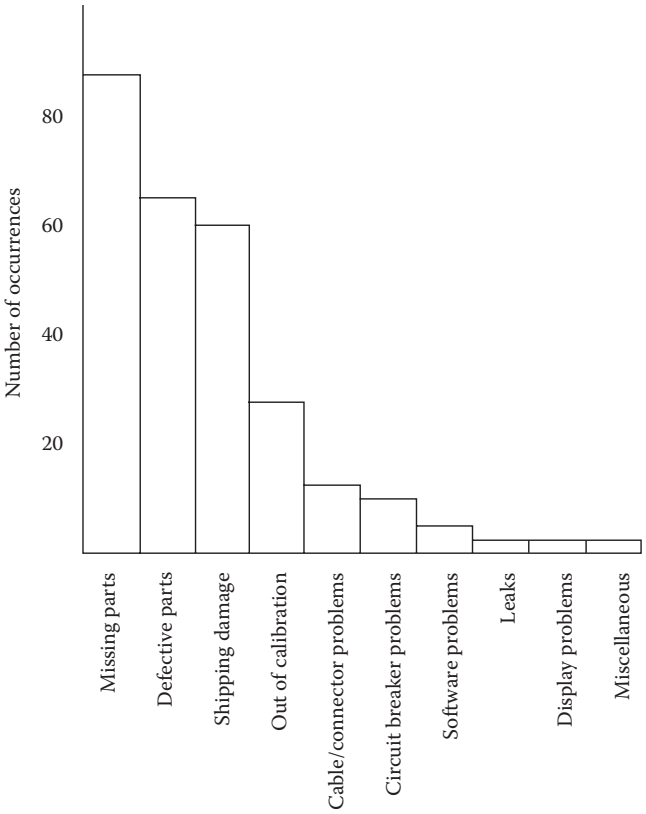

FIGURE 14.7 Pareto analysis.

14.9.1 Pareto Analysis

Pareto analysis is a plot of individual failures versus the frequency of the failures. The individual failures are listed on the *x*-axis and the frequency of occurrence on the *y*-axis. The result is a histogram of problems and their severity. The problems are usually plotted with the most frequent on the left. Once the results are obtained, appropriate action can be taken. Figure 14.7 is an example of a Pareto analysis based on the following data:

Problem	Frequency
Power supply problems	10
Leaks	8
Defective parts	75
Cable problems	3
Missing parts	42
Shipping damage	2

14.9.2 Graphical Plotting

When plotting data, time is usually listed on the *x*-axis and the parameter to be analyzed on the *y*-axis.

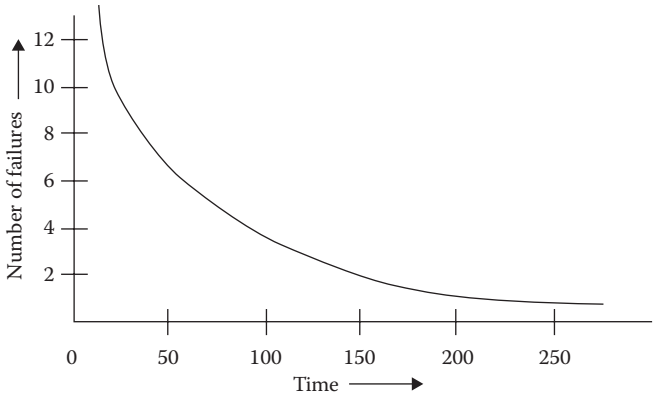

FIGURE 14.8 Plot of field data.

Example 14.10

Nerve stimulators were subjected to 72 hours of burn-in at ambient temperature prior to shipment to customers. Reports of early failures were grouped into 50-hour intervals and showed the following pattern:

Hourly Increment	Number of Failures
0–50	12
51–100	7
101–150	4
151–200	1
201–250	1

Figure 14.8 is a plot of the data. The data indicate that the number of failures begins to level off at approximately 200 hours. The burn-in was changed to an accelerated burn-in, equal to 300 hours of operation.

14.9.2.1 Weibull Plotting

Weibull paper is a logarithmic probability plotting paper constructed with the *y*-axis representing the cumulative probability of failure and the *x*-axis representing a time value, in hours or cycles. Data points are established from failure data, with the failure times arranged in increasing order or value of occurrence. Corresponding median ranks are assigned from a percent rank table, based on the sample size. The logarithmic nature of typical failure rates allows one to extrapolate future failure rates for the studied device.

EXERCISES

1. Almost 50 switches are placed on test to be terminated after each switch has completed 1000 cycles of "on" and "off." Five switches fail at the following times: 650, 925, 2000, 3500, and 7500 cycles. What is the failure rate of the switches in failures per million cycles?
2. Nearly 10 oximeters are placed on test. They are to complete 5000 hours of operation. Test results are listed below. Every failed unit is replaced immediately. What is the MTBF?

Unit Number	Time of Failure (Hours)
1	800
2	No failure
3	1000 and 1250
4	2200
5	No failure
6	850 and 3200
7	550
8	No failure
9	4200
10	925 and 3350

3. Using the test data from exercise 2, calculate the MTBF when the failed units are not replaced. Compare the results of exercises 2 and 3.
4. About 50 power supplies were tested for 3000 hours. No failures were observed during the test. Determine the MTBF at a 95% confidence level.
5. A resistor has a failure rate of 0.0052 failures per million hours. Calculate the reliability of the resistor for an operating period of 10,000 hours.
6. A ventilator has a reliability of 99.999 for a mission time of 20,000 hours. What is the MTBF?
7. Use the data in exercise 2 to determine the upper and lower confidence limits at a 95% confidence level.
8. Repeat exercise 7 using a 90% confidence level. Compare the results of the two confidence levels.
9. Power supplies were subjected to 168 hours of burn-in with the failures occurring at 10, 22, 35, 38, 42, 45, 48, 52, 63, 77, 88, 94, 122, 135, 148, and 165 hours. Plot the data in appropriate intervals to show the failure pattern. Discuss the possible actions that would result from the plot.
10. Using the results from exercise 1, determine the MTBF for the switches. The metric for the MTBF will be in cycles.

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15 Product Liability and Accident Investigations

Why is there never enough time to develop a product correctly, but always enough time to do it over?

Anonymous

An error doesn't become a mistake until you refuse to correct it.

Orlando A. Battista

Earlier chapters covered reliability, which, with proper design, should imply safety. This chapter will cover the legal aspects of liability, and to tie these issues together, a number of legal cases will be covered, with the intention of informing the reader regarding items that must be considered in the design of safe medical devices and systems. The cases will also inform as to the readers' possible future as a forensics or accident investigation engineer.

15.1 PRODUCT LIABILITY LAWS

The law can be defined as the collection of rules and regulations by which society is governed. The law regulates social conduct in a formal binding way while it reflects society's needs, attitudes, and principles. Law is a dynamic concept that lives, grows, and changes. It can be described as a composite of court decisions, regulations, and sanctioned procedures, by which laws are applied and disputes adjudicated. As of this writing, it is an evolving, somewhat imperfect embodiment of our societies' concept of ethics in interpersonal matters.

Negligence, strict liability, and breach of warranty are the three most common theories of liability for which a manufacturer of a product or a provider may be held liable. The result of this is termed a "tort," or personal injury. The personal injury (damages) may involve pain, anguish, additional expenses, lost work time, loss of consortium, and so forth. These theories are referred to as common-law causes of action, which are distinct from causes of action based on federal or state statutory law, such as the bases for Food and Drug Administration (FDA) enforcement actions. Although federal legislative action has been considered that would create a uniform federal product liability law and has been proposed and debated, no such law exists today. Thus, such litigation is governed by the laws of each state.

These three doctrines are called "theories of recovery" because an injured person cannot recover damages against a defendant unless he/he alleges and proves, through use of one or more of these theories, that the defendant owed him a legal duty and that the defendant breached that duty, thereby causing the plaintiff's injuries. Although each is conceptually distinct, similarities exist between them. Indeed, two or more theories are asserted in many product defect suits.

15.1.1 Negligence

Since much of medical malpractice litigation relies on negligence theory, it is important to clearly establish the elements of that cause of action. Negligence may be defined as conduct that falls below

the standard established by law for the protection of others against unreasonable risk of harm. Four major elements form the basis for the negligence claim:

- That a person or business owes a duty of care to another
- That the applicable standard for carrying out the duty be breached (such as a failure to treat or diagnose)
- That as proximate cause of the breach of duty, a compensable injury results
- That there be compensable damages or injury to the plaintiff ("injured party")

The burden is on the plaintiff (with the assistance, normally of a lawyer, and others as needed) to establish each and every element of the negligence action.

The basic idea of negligence law is that one should have to pay for injuries that he/she causes when acting below the standard of care of a reasonable, prudent person participating in the activity in question. This standard of conduct relates to a belief that centers on potential victims: that people have a right to be protected from unreasonable risks of harm. A fundamental aspect of the negligence standard of care resides in the concept of foreseeability.

A plaintiff in a product liability action grounded in negligence, then, must establish a breach of the manufacturer's or seller's duty to exercise reasonable care in the manufacture and preparation of a product (or process). The manufacturer, in particular, must be certain that the product is free of any potentially dangerous defect that might become dangerous upon the happening of a reasonably anticipated emergency. The obligation to exercise reasonable care has been expanded to include reasonable care in the inspection or testing of the product, the design of the product, or the giving of warnings concerning the use of the product.

A manufacturer must exercise reasonable care even though he/she is but a link in the production chain that results in a finished product. For example, a manufacturer of a product that is designed to be a component part of another manufactured product is bound by the standard of reasonable care. Similarly, a manufacturer of a finished product that incorporates component parts fabricated elsewhere has the same legal obligation.

A seller of a product, on the other hand, is normally held to a less stringent standard of care than a manufacturer. The lesser standard is also applied to distributors, wholesalers, or other middlemen in the marketing chain. This rule pertains because a seller or middleman is viewed as simply a channel through which the product reaches the consumer. It does not excuse the seller or distributor from a lawsuit if the product has been shown to be defective.

In general, the duty owed at any particular time varies with the degree of risk involved in a product. The concept of reasonable care is not static but changes with the circumstances of the individual case. The care must be commensurate with the risk of harm involved. Thus, manufacturers or sellers of certain hazardous products must exercise a greater degree of care in their operations than manufacturers or sellers of other less dangerous products.

15.1.2 Strict Liability

Unlike the negligence suit, in which the focus is on the defendant's conduct, in a strict liability suit, the focus is on the product itself. The formulation of strict liability states that one who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his/her property is subject to liability for physical harm thereby caused to the ultimate user or consumer or to his/her property if the seller is engaged in the business of selling such a product, and it is expected to and does reach the user or consumer without substantial change to the condition in which it is sold. Therefore, the critical focus in a strict liability case is on whether the product is defective and unreasonably dangerous. A common standard applied in medical device cases to reach that determination is the risk/benefit analysis—that is, whether the benefits of the device outweigh the risks attendant with its use.

The result of strict liability is that manufacturers, distributors, and retailers are liable for the injuries caused by defects in their products, even though the defect may not be shown to be the result of any negligence in the design or manufacture of the product. Moreover, under strict liability, the manufacturer cannot assert any of the various defenses available to him/her in a warranty (guarantee) action (see Section 15.1.3).

Strict liability means that a manufacturer may be held liable even though he/she has exercised all possible care in the preparation and sale of this product. The sole necessity for manufacturer liability is the existence of a defect in the product and a causal connection between this defect and the injury that resulted from the use of the product.

15.1.3 Breach of Warranty

A third cause of action that may be asserted by a plaintiff is breach of warranty. A warranty action is contractual rather than tortuous in nature. Its basis lies in the representations, either express or implied, that a manufacturer or a seller makes about its product.

There are three types of breaches of warranty that may be alleged:

1. Breach of the implied warranty of merchantability
2. Breach of the implied warranty of fitness for a particular purpose
3. Breach of an express warranty

15.1.3.1 Implied Warranties

Some warranties accompany the sale of an article without any express conduct on the part of the seller. These implied warranties are labeled the warranties of merchantability and of fitness for a particular purpose.

A warranty that goods shall be merchantable is implied in a contract for their sale, if the seller is a merchant who commonly deals with such goods. At a minimum, merchantable goods must

- Pass without objection in the trade under the contract description
- Be fit for the ordinary purposes for which they are used
- Be within the variations permitted by the sales agreement, of even kind, quality, and quantity within each unit and among all units involved
- Be adequately contained, packaged, and labeled as the sales agreement may require
- Conform to the promises or affirmations of fact made on the container or label

The implied warranty of fitness for a particular purpose arises when a buyer makes known to the seller the particular purpose for which the goods are to be used, and the buyer, relying on the seller's skill or judgment, receives goods that are warranted to be sufficient for that purpose.

15.1.3.2 Exclusion of Warranties

The law has always recognized that sellers may explicitly limit their liability upon a contract of sale by including disclaimers of any warranties under the contract. The Uniform Commercial Code (United States) embodies this principle and provides that any disclaimer, exclusion, or modification is permissible under certain guidelines. However, a disclaimer is not valid if it deceives the buyer.

These warranty causes of action do not offer any advantages for the injured plaintiff that cannot be obtained by resorting to negligence and strict liabilities claims and, in fact, pose greater hurdles to recovery. Thus, although a breach of warranty claim is often pled in the plaintiff's complaint, it is seldom relied on at trial as the basis for recovery.

15.1.4 Defects

The term "defect" is used to describe generically the kinds and definitions of things that courts find to be actionably wrong with products when they leave the seller's hands. In the decisions, however, the courts sometimes distinguish between defectiveness and unreasonable danger. Other considerations in determining defectiveness are as follows:

- Consumer expectations
- Presumed seller knowledge
- Risk–benefit balancing
- State of the art
- Unavoidably unsafe products

A common and perhaps the prevailing definition of product unsatisfactoriness is that of "unreasonable danger." This has been defined as that the article sold must be dangerous to an extent beyond that which would be contemplated by the ordinary consumer who purchases it, with the ordinary knowledge common to the community as to its characteristics.

Another test of defectiveness sometimes used is that of presumed seller knowledge: would the seller be negligent in placing a product on the market if he/she had knowledge of its harmful or dangerous condition? This definition contains a standard of strict liability, as well as one of defectiveness, since it assumes the seller's knowledge of a product's condition even though there may be no such knowledge or reason to know.

Sometimes, a risk–benefit analysis is used to determine defectiveness, particularly in design cases. The issue is phrased in terms of whether the cost of making a safer product is greater or less than the risk or danger from the product in its present condition. If the cost of making the change is greater than the risk created by not making the change, then the benefit or utility of keeping the product as is outweighs the risk, and the product is not defective. If, on the other hand, the cost is less than the risk, then the benefit or utility of not making the change is outweighed by the risk, and the product in its unchanged condition is defective.

Risk–benefit or risk–burden balancing involves questions concerning state of the art, since the burden of eliminating a danger may be greater than the risk of that danger if the danger cannot be eliminated. State of the art is similar to the unavoidably unsafe defense where absence of the knowledge or ability to eliminate a danger is assumed for purposes of determining if a product is unavoidably unsafe. "State of the art" is defined as the state of scientific and technological knowledge available to the manufacturer at the time the product was placed in the market.

Determining defectiveness is one of the more difficult problems in product liability, particularly in design litigation. There are three types of product defects:

1. Manufacturing or production defects
2. Design defects
3. Defective warnings or instructions

The issue implicates questions of the proper scope of the strict liability doctrine, and the overlapping definitions of physical and conceptual views of defectiveness.

Manufacturing defects can rarely be established on the basis of direct evidence. Rather, a plaintiff who alleges the existence of a manufacturing defect in the product must usually resort to the use of circumstantial evidence in order to prove that the product was defective. Such evidence may take the form of occurrence of other similar injuries resulting from use of the product, complaints received about the performance of the product, defectiveness of other units of the product, faulty methods of production, testing or analysis of the product, elimination of other causes of the accident, and comparison with similar products.

A manufacturer has a duty to design his/her product so as to prevent any foreseeable risk of harm to the user or patient. A product that is defectively designed can be distinguished from a product containing a manufacturing defect. While the latter involves some aberration or negligence in the manufacturing process, the former encompasses improper planning in connection with the preparation of the product. Failure to exercise reasonable care in the design of a product is negligence. A product that is designed in a way that makes it unreasonably dangerous will subject the manufacturer to strict liability. A design defect, in contrast to a manufacturing defect, is the result of the manufacturer's conscious decision to design the product in a certain manner.

Product liability cases alleging unsafe design may be divided into three basic categories:

- Cases involving concealed dangers
- Cases involving a failure to provide appropriate safety features
- Cases involving construction materials of inadequate strength

A product has a concealed danger when its design fails to disclose a danger inherent in the product that is not obvious to the ordinary user.

Some writers treat warning defects as a type of design defect. One reason for doing this is that a warning inadequacy, like a design inadequacy, is usually a characteristic of a whole line of products, while a production or manufacturing flaw is usually random and atypical of the product. (Reminder: the FDA requires documentation of products [labeling and usage]; thus, this information may be entered as evidence [Chapter 16.] The FDA mandated Medical and User Device Experience [MAUDE] database [see Chapters 16 and 17] reports may also be used in court.)

15.1.5 Failure to Warn of Dangers

An increasingly large portion of product liability litigation concerns the manufacturer's or seller's duty to warn of actual or potential dangers involved in the use of the product. Although the duty to warn may arise under all three theories of product liability, as mentioned, most warnings cases rely on negligence principles as the basis for the decision. The general rule is that a manufacturer or seller who has knowledge of the dangerous character of the product has a duty to warn users of this danger. Thus, failure to warn where a reasonable man would do so is negligence.

15.1.6 Plaintiff's Conduct

A manufacturer or seller may defend a product liability action by demonstrating that the plaintiff either engaged in negligent conduct that was a contributing factor to his injury or used a product when it was obvious that a danger existed and thereby assumed the risk of his injury. Another type of misconduct that may defeat recovery is when the plaintiff misuses the product by utilizing it in a manner not anticipated by the manufacturer. The applicability of these defenses in any given product suit is dependent upon the theory or theories of recovery that are asserted by the plaintiff.

15.1.7 Defendant's Conduct

Compliance with certain standards by a manufacturer may provide that party with a complete defense if the product leaves the manufacturer's or seller's possession or control and when it is a substantial or proximate cause of the plaintiff's injury. Exceptions to this rule include alterations or modifications made with the manufacturer's or seller's consent or according to manufacturer's/seller's instructions.

15.1.8 Defendant-Related Issues

When a medical device proves to be defective, potential liability is created for many parties who may have been associated with the device. Of all the parties involved, the injured patient is least

able to bear the financial consequences. To place the financial obligation upon the proper parties, the courts must consider the entire history of the product involved, often from the time the design concept was spawned until the instant the injury occurred. The first parties encountered in this process are the designers, manufacturers, distributors, and sellers of the product.

Physicians and hospitals are subject to liability through medical malpractice actions for their negligence, whether or not a defective product is involved. Where such a product is involved, the doctor or hospital may be liable for the following:

- Negligent misuse of the product
- Negligent selection of the product
- Failure to inspect or test the product
- Using the product with knowledge of its defect

Negligent selection may often involve the assertion that the device/process is not "state of the art."

15.1.9 Manufacturer's and Physician's Responsibilities

Manufacturers of medical devices have a duty with regard to manufacture, design, warnings, and labeling. A manufacturer is required to exercise that degree of care that a reasonable, prudent manufacturer would use under the same or similar conditions. A manufacturer's failure to comply with the standard in the industry, including failing to warn or give adequate instructions, may result in a finding of liability against the manufacturer.

With regard to medical devices, a manufacturer must take reasonable steps to warn physicians of dangers of which it is aware or reasonably should be aware where the danger would not be obvious to the ordinary competent physician dispensing a particular device. The responsibility for the prudent use of the medical device is with a physician or other designated caregiver. A surgeon who undertakes to perform a surgical procedure has the responsibility to act reasonably.

It is therefore required of the manufacturer to make a full disclosure of all known side effects and problems with a particular medical device by use of appropriate warnings given to physicians. The physician is to act as the learned intermediary between the manufacturer and the patient and transmit appropriate information to the patient. The manufacturer, however, must provide the physician with the information in order that he/she can pass it on to the patient.

In addition, the manufacturer's warnings must indicate the scope of potential danger from the use of a medical device and the risks of its use. This is particularly important where there is "off-label use" (the practice of using a product approved for one application in a different application) by a physician.

The manufacturer's warnings must detail the scope of potential danger from the use of a medical device, including the risks of misuse. The warnings must alert a reasonably competent physician to the dangers of not using a product as instructed. It would seem then the manufacturer may be held liable for failing to disclose the range of possible consequences of the use of a medical device if it has knowledge that the particular device is being used "off label."

The duty of a manufacturer and physician for use of a medical device will be based upon the state of knowledge at the time of use. The physician therefore has a responsibility to be aware of the manufacturer's warnings as he/she considers the patient's condition. This dual responsibility is especially relevant in deciding what particular medical device to use. Physician judgment and an analysis of the standard of care in the community should predominate (/) the court's analysis in determining liability for possible misuses of the device.

A concern arises if the surgeon has received instruction as to the specific device from a manufacturer outside an investigative device exemption (IDE) clinical trial approved by the FDA. In such circumstances, plaintiffs will maintain that the manufacturer and physician conspired to promote a product that is unsafe for "off-label use."

15.2 ACCIDENT RECONSTRUCTION AND FORENSICS

Biomedical engineers, due to their generally broad-based education and familiarity with medical devices as well as the physiology and biomechanics of the human, may sometimes be called upon to analyze accidents and testify in court cases. With proper credentials (experience with the device or process or situation, licensing, etc.), persons who do (in any field) this are termed expert witnesses. This section of the chapter will cover the analysis of several medical device accidents, followed by a brief discussion on biomechanics and accident (physical injury due to impact by car and so forth) investigations. Both of these have implications for improved designs of devices and processes that biomedical engineers may be involved in.

15.2.1 Medical Device Accident Investigations

A medical device accident investigation follows a fairly typical chain of events, of which most are in common for accidents in general. The overall process for a medical device accident investigation takes roughly the following outline:

- An incident occurs, someone is injured, and a cause for action is established.
- You are contacted by the wronged person, by his/her lawyer, or by one of the parties or his/her representative needing an investigation.
- After an initial familiarization with the problem, you may opt to work on the problem or opt out.
- You need to collect data. This means you must inspect the equipment and scene (if any), photograph and/or sketch the environment as necessary, gather evidence, and read whatever written documentation exists at this point. This may include operative notes, nurses' notes, some preliminary testimony, machine charts, and so forth.
- You need to research the device or process in question. This means that you will use MAUDE if necessary. You will need to access the operator's manual for the device, as necessary. You will need to investigate maintenance manuals, if necessary. You may need to run simulations on the device, if necessary. You likely will need to use the web, other than just MAUDE, for key word searches. You may need to obtain agreement for the use of specialists, such as personnel who perform calibration or maintenance on the devices as necessary. You may need to do some basic research and mock-ups of the device as necessary.
- As a result of your work, you will need to estimate causes and their likelihood. If you can demonstrate the error, so much the better.
- A branching point is reached here. A report (oral or written, this should be pre–agreed to) should be submitted to the person who contacted and contracted you. You must be prepared to continue the investigation, await further court action, or be released from further work. The latter is generally the case when you find for someone other than those who hired you.
- You must be prepared to answer questions from opposition lawyers if necessary. This can take the form of both oral and written testimony as to the current status of the investigation. Your notes may be subpoenaed and copied in their entirety by the opposition party if Rule 26 (Federal Law) is invoked. (The intent of Rule 26 is to ensure that expert's planned testimony is known well in advance of a court appearance, that there be the ability to determine that there indeed is a justified case rather than a frivolous lawsuit in progress, and to decrease the need for pretrial maneuvering.)
- Most of the time, a final formal report designating your findings and estimating fault will end your work. On a small number of occasions, expect to go to court, get sworn in, and testify regarding your work.

Several brief cases will serve to illustrate the range of efforts that may come of a medical device accident investigation.

15.2.1.1 Enteral Feeding Tube Complication

An elderly male patient was sent home from a nursing facility with an enteral feeding pump (direct-to-stomach tube feeding), a supply of feeding compound, and a supply of enteral feeding pump tubes. On the first use of the pump, the patient wound up with too high a flow of food such that food filled the stomach and entered the lungs. He expired due to pneumonia induced by the flow within a few days.

Lawsuits were filed against the skilled nursing facility, the makers of the enteral feeding tube, the makers of the enteral feeding apparatus (pump mechanism), the physician involved, and so forth. After a very brief overview of the material, the manufacturer of the enteral feeding apparatus suggested a panel meeting of all involved parties under Rule 26, in order to attempt to place blame and suggest a method of discovery if necessary. A panel was convened comprised of representatives of the nursing facility, a biomedical engineer from academia (King), a representative from the company that manufactured the pump, and the opposition lawyers. Within 5 minutes, the determination was made that the pump had been sent home with the wrong manufacturers' pump tubing installed. The tubing that was in place allowed for gravity feed of the feeding fluid independent of the pump speed. Thus, a direct cause of the accident was found in a timely manner. The case continued without the biomedical engineer, as the cause of the accident was evident; the question that remained was only one of who sent the wrong materials.

15.2.1.2 Pressure-Limited Respiration System

A pressure-limited pump was used to ventilate a very young child who had a very small plastic airway directly in place in the throat (tracheotomy tube). The child was found asphyxiated after the airway had withdrawn from the child. The unit, though the nursing service has presumably properly set the upper and lower pressure controls, was not alarming.

The unit was obtained and taken to a clinical engineering service to be tested. All testing was videotaped. Without the tracheotomy tube in place, the device alarmed. It was determined that the extremely small airway element enabled sufficient backpressure to the system that the recommended pressure settings were meaningless. With the tracheotomy tube in place, the unit did not alarm and continued ventilating "nothing."

It was surmised that the child managed to move and dislodge the tracheotomy tube while being ventilated. Without the lower pressure alarm being set with this disconnection pressure, the unit would never alarm. No adequate information could be found in the operator's manual to account for such a situation. A report indicating these facts was submitted; the nursing service and the ventilator manufacturer settled out of court.

It is worth noting that ventilators that rely only on pressure alarms are thus not necessarily safe in disconnected and pinched tubing settings. A far better alarm system for a patient ventilator will use both pressure alarm settings and CO_2 waveform detection. If the CO_2 waveform is not evident—the alarms must be sounded—the patient is either disconnected or not breathing (apneic).

15.2.1.3 Intramedullary Nail Accident

A veterinarian was using a commercially available chuck system that held a double pointed intramedullary rod for insertion into the broken femur of a fairly large dog. The chuck (similar to those used on hand drills) used a friction system to hold the rod in place. There was a short section of tubing at the back end of the chuck to keep the nail straight during insertion.

The veterinarian was overly hasty in his attempt at insertion of the rod; instead of using a hammer at the end of the tubing on the insertion device, he used his hand. The rod went through his hand (slipping through the chuck), putting him out of business as a vet for several months. He sued for pain and suffering and lost income.

In the ensuing court case, the lack of a backstop for the intramedullary rod was pointed out as a design flaw by plaintiff's expert witness. However, it was presented by the defense that there were clear instructions with the insertion device as to its use with a hammer or other safe impact facilitation devices and that he further had been instructed in veterinarian school as to the proper use of the device. He lost his case and was further instructed to pay all court costs.

15.2.1.4 To Assist in a Suit, or Not?

Circa 1993, author King was asked to investigate and to be an expert witness for a case involving multiple failed operations. Specifically, the case involved a man who had had three successive failed penile implants. The implants were of a pump-type mechanism for the purposes of male "enhancement" when natural mechanisms fail.

After a very brief investigation, the case was refused by the author. At the time, the specific operation done was only successful 75% of the time. Each time, the patient had signed an operative consent form that had indicated that he had a 25% chance of failure. After three operations, he was still at a risk of failure at the 1.56% level (1/64). He had successively and knowingly signed on to a surgery with a high risk of failure and thus did not have a case in the eyes of this author.

15.2.1.5 Counterexample

An elderly female patient had hip replacement surgery in late 2005 with a prosthesis that had been implicated in several failures at the time of the later lawsuit. Within 3 months, the patient had to have revision surgery. Two months later, another revision needed to be done. Seventeen months later, another revision needed to be done (2007). All four operations were done by the same physician; all four operations involved the same prosthesis brand. A lawsuit was filed by 2008 against both the physician and the manufacturer of the prosthesis.

To estimate the approximate failure rate of the prosthesis, one might conservatively estimate a lifetime of 10 years (120 months). One can use reliability calculations (see Chapter 12), or for a very rough estimate, one can use a constant failure rate each month, so that the chance of failure in 2 months with a device that is expected to last 120 is simply 2/120, or one chance in 60. For the successive failures shown here, a rough estimate of the chance of failure of this device (prosthesis) is about 1 in 17,000, which is not very likely.

MAUDE data for 2005 and 2006 indicated that there were 20 complaints for all similar prostheses implanted during those 2 years *and* prior. As 2 of those 20 complaints had to be from this one patient/provider/manufacturer combination, a logical conclusion should have been was that the physician was at fault. Indeed, the physician was sued for malpractice.

15.2.1.6 Blood Oxygenator Malfunction

A patient was on a heart–lung machine during open-heart surgery. A portion of the device was a holding/oxygenation system that was designed with an ultrasonic high-level blood detection system and two low-level (low, lower) ultrasonic detection systems. The system was designed to alarm on the high and low level of blood in the device. The lowest level of the blood alarm system was designed to shut off the pump system entirely.

The system additionally had a sensor on the return line to the patient; this sensor was an infrared detection system. This sensor would only operate if there were no color in the return line (straight Ringer's solution, for example); it would not alarm if it "saw" foamy blood or normal blood.

The first set of ultrasonic alarms could be turned off during the start of any procedure such that the alarms would not bother the surgeon and other staff. Likewise, they could be turned off when the surgeon needed special low flow or other similar conditions.

According to hand-kept records, there was one case where a patient received an air embolus during on-pump surgery; no alarms sounded. The patient died. A lawsuit ensued.

The records were inspected for probable cause, as were the device and preliminary testimony. Two design flaws stood out. First, the alarms on the level of the blood could be turned off even if

the surgical conditions requiring low flow ended; thus, increased vigilance on the part of the pump operator was required. It is likely that the pump operator failed to turn the alarms back on when the pump was returned to full flow (no "fail-safe" design). For the flow rates that were common during the majority of the operation, it would have required only 1.4 seconds of time to completely empty the blood reservoir. Having done so, foam and air would have been passing by the final alarm device—the infrared detector prior to the patient. The second design flaw was the use of the infrared system—which could be fooled by foam. A state-of-the-art device would have used a final ultrasonic blood detection system at this point as they are virtually foolproof.

This case was settled out of court.

15.2.1.7 Failure to Monitor

A patient suffering heart palpitations and dizziness was admitted to an overcrowded hospital environment. The patient was placed on a gurney and screened off from public view. The patient was connected to a computerized vital signs monitoring system that was connected to the local area network and a central monitoring network.

The patient was found dead the next morning due to cardiac arrest. The next of kin began a lawsuit.

An inspection of records showed that the monitor had a function called "admit patient"; this function was never initiated. Thus, the patient was never monitored.

This case was settled out of court. The monitoring system has been redesigned.

15.2.1.8 Failure to Perform, Period

A ventilator was in use on a small child during transport in a private vehicle. The ventilator was being powered via a cord inserted into the cigarette light socket. The air conditioning system in the car was in use. The caretakers noted after a time (>30 minutes) that the child was not being ventilated and was turning blue. No alarms were sounding. Emergency care was immediately attempted; an initial return to normal ventilation was noted. The child died within a few days, however, due to this injury.

An inspection of the data log for this device indicated that it was rebooting for a period of ~20 minutes during the time of the incident. It was surmised that this was due to a poor connection with the car via the cigarette lighter, or poor power filtering of spikes from the car power system (and thus interference with the ventilator computer system).

This case was settled out of court for the plaintiffs. Of interest is the fact that the company recalled their supplied (car) power cords about this same time. This recall was followed by a recall of most of their devices for replacement of the power supply board on their systems.

15.2.2 Biomechanics and Traffic Accident Investigations

A very basic understanding of biomechanics is necessary prior to any undertaking in which a bioengineer may be involved in vehicle accident investigation. Some of the concepts that need to be understood are the following:

Data collection: data for analyses involving traffic accidents involve data collected from reported and analyzed accidents. Large data sets are collected by individual states, some of which are recollected and analyzed by the National Highway Transportation Safety Administration (NHTSA, http://www.hhtsa.gov). The agency also specifically maintains data on fatal accidents, including information on vehicle type, rollover, ejection, alcohol use, and so forth. A smaller data set includes data for cases specifically investigated by the agency, data that include medical information as well as more specific conclusions as to the cause of the accident, and many other details. Other related data sets have been obtained from cadaver studies, anthropometrical dummy studies, animal studies, and mathematical

modeling analyses. Much of the data obtained and related issues may be found on the NHSTA website and in the *Proceedings of the Annual STAPP Car Crash Conference* (see http://www.stapp.org pubs.shtml for ordering information).

Injury estimation: In studies of human survival following trauma, an early scheme involved the development of an abbreviated injury scale (AIS); this scale ranges from 0 (minor sprain) to 6 (unsurvivable injury). This scale is developed for each of the six body regions of interest in survivability, the head, face, chest, abdomen, extremities (including pelvis), and external. The highest squared scores from the three most injured areas are added together to generate a new score, the Injury Severity Score (ISS). With the exception that any AIS rating of 6 automatically yields the maximum ISS score of 75, this score relates linearly to rates of mortality, morbidity, and length of hospital stay.[1]

Impact analyses: Often, an engineer must estimate the relative speeds of the vehicles and personnel involved. This means that the engineer must, from the data involved in the accident report, crush patterns on the vehicles involved, vehicle data sheets, weather conditions reported, and so forth, and estimate the relative speeds, angles of impact, and probable outcome of an accident. For example, working backward from skid length data, one can find that a vehicle's initial velocity prior to the skid is directly related to the square root of twice the product of skid length, skid friction coefficient, and the value of gravity, or "g." The skid friction coefficient is a function of the type of surface (pavement vs. dirt road, for example), the weather conditions (dry, wet, or icy); and the type of braking system the vehicle has (2 or 4 wheel, antilock, etc.). If a subject has been thrown or ejected from a vehicle, simple trajectory analysis can be used to determine the initial velocity, if sufficient information exists. If there is little body damage on two vehicles, a combination of conservation of momentum analysis and elastic collision analysis might apply, along with skid analysis. Alternatively, damage analysis combined with inelastic collision analysis must be used. Most vehicular accident experts use software modeling techniques that imbed the previous data with whole-body simulation software to estimate the cause(s) of injury.

The biomedical engineer doing design or doing forensic analysis after the fact on matters involving vehicular accidents must understand this and be able to apply background material learned in a biomechanics class to real-life problems. A few examples follow:

- Occupant restraint systems may be designed to absorb energy during an impact. Consider the alternatives for air bags, especially for situations with low-body-weight passengers.
- During a motorcycle–truck accident, the helmet of the motorcyclist came off, resulting in death of the motorcyclist due to blunt head trauma. Where was the error in the design of the helmet system?
- Current seat belts are a trade-off between convenience and safety. Determine the "ideal" design.

One case example will enforce the aforementioned. A husband and wife were in a private vehicle (a van), stopped near the midline of a road, waiting to turn into a driveway. Both claimed to have been belted in. They were rear-ended by another vehicle, which was traveling at excessive speed. The wife (passenger) wound up in the inside back of the vehicle, severely injured. The driver (husband) had minor injuries.

A lawsuit ensued against the manufacturer of the vehicle that the husband/wife team occupied. An investigation into the design of the vehicle turned up the fact that the wife's hand could have struck the seatbelt release button (due to the rear impact and the poor design of the seatbelt locking mechanism), thus releasing her to fly about the cabin due to this release.

This case was settled out of court.

15.3 CONCLUSION

Product and process liability will undoubtedly continue to be a controversial field of law, because it cuts across so many fundamental issues of our society. It will also remain a stimulating field of study and practice, since it combines a healthy mixture of the practical and theoretical. The subject will certainly continue to change, both by statutory and by common law modification.

Product liability implicates many of the basic values of our society. It is a test of the ability of private industry to accommodate competitiveness and safety. It tests the fairness and the workability of the tort system of recovery and of the jury system as a method of resolving disputes.

EXERCISES

1. Visit the new car assessment pages at the NHTSA website; query the database for the number of deaths per accident for a given (recent) year. Comment on your results.
2. Visit the Stapp Conference website (http://www.stapp.org); determine the history of the conferences.
3. Do a MAUDE search for deaths caused by Enteral Feeders. Print out and discuss at least one case.
4. Do a MAUDE search for deaths caused in 1 week of the year. Comment on your results.
5. One of the authors of this book owns both a Honda Fit and a Honda CRV from the 2007–2008 model years. Determine, by any method (explain), which is the safer car for the driver.
6. Find data for the chance of survival for a patient with a major liver laceration and a closed tibial fracture as a result of a vehicular injury.
7. A lawyer asks you to testify about an injury that was received during a low-speed (10 mph or less) two-vehicle collision. Specifically, he asks that you testify that no data exist that can prove the correct speeds of the vehicles and the likelihood of injury. Is this correct?
8. A 3-year-old female sustained neck injuries on a child roller coaster at a theme park. What would you do to prove or disprove this claim? By the way, the father has a videotape of the injury occurring, and the girl seemed to have a "long neck." This particular ride had been in use for 10 years.
9. A child sustained a severe cut on his nose due to him falling off of a motorbike. The helmet he was wearing caused the cut. What was the design flaw here, and who was at fault?
10. Find and report on the use of the Apgar score. How would you use this data in a lawsuit against a hospital?
11. The brain poses a special case when studying injury patterns. Research the term *contrecoup*; report on its significance.

REFERENCE

1. http://www.trauma.org for more information.

SUGGESTED READING

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16 The FDA and Devices

> There is a greater law than the FDA and that is an obligation of a doctor to try to do anything he can to save a life when he thinks there is a chance.
>
> **Dr. Cecil Vaughn**

The Food and Drug Administration (FDA) of the United States was first formed in 1906 in response to the then rampant interstate commerce in misbranded food, drink, and drugs. Of primary interest to designers of devices and systems will be the regulations involving medical devices, the subject of this chapter. The history of the FDA, a discussion of drug development and the role of the FDA in this, and the subject of combination devices (drug/device) will be the subject of Chapter 17.

When designing any device that will be used medically, it is important to consider all safety aspects, including the repercussions of design flaws and misuse of the device. Regulation of medical devices is intended to protect consumers' health and safety by attempting to ensure that marketed products are effective and safe. Prior to 1976, the FDA had limited authority over medical devices under the Food, Drug, and Cosmetic Act of 1938. Beginning in 1968, Congress established a radiation control program to authorize the establishment of standards for electronic products, including medical and dental radiology equipment. From the early 1960s to 1975, concern over devices increased, and six U.S. presidential messages were given to encourage medical device legislation.

In 1969, the Department of Health, Education, and Welfare appointed a special committee (the Cooper Committee) to review the scientific literature associated with medical devices. The committee estimated that over a 10-year period, 10,000 injuries were associated with medical devices, of which 731 resulted in death. The majority of problems were associated with three device types: artificial heart valves, cardiac pacemakers, and intrauterine contraceptive devices. There activities culminated in passage of the Medical Devices Amendments of 1976.

Devices marketed after 1976 are subject to full regulation unless they are found substantially equivalent (they are "grandfathered") to a device already on the market in 1976. By the end of 1981, only about 300 of the 17,000 products submitted for clearance to the FDA after 1976 had been found not substantially equivalent.

16.1 HISTORY OF DEVICE REGULATION

In 1906, the FDA enacted its first regulations addressing public health. While these regulations did not address medical devices per se, they did establish a foundation for future regulations. It was not until 1938, with the passage of the Federal Food, Drug, and Cosmetic (FFD&C) Act, that the FDA was authorized, for the first time, to regulate medical devices. This act provided for regulation of adulterated or misbranded drugs, cosmetics, and devices that were entered into interstate commerce. A medical device could be marketed without being federally reviewed and approved.

In the years following World War II, the FDA focused much of the attention on drugs and cosmetics. Over-the-counter drugs became regulated in 1961. In 1962, the FDA began requesting safety and efficacy data on new drugs and cosmetics.

By the mid-1960s, it became clear that the provisions of the FFD&C Act were not adequate to regulate the complex medical devices of the times to assure both patient and user safety. Thus, in

1969, the Cooper Committee was formed to examine the problems associated with medical devices and to develop concepts for new regulations.

In 1976, with input from the Cooper Committee, the FDA created the Medical Device Amendments to the FFD&C Act, which were subsequently signed into law. The purpose of the amendments was to assure that medical devices were safe, effective, and properly labeled for their intended use. To accomplish this mandate, the amendments provided the FDA with the authority to regulate devices during most phases of their development, testing, production, distribution, and use. This marked the first time the FDA clearly distinguished between devices and drugs. Regulatory requirements were derived from this 1976 law.

In 1978, with the authority granted the FDA by the amendments, the Good Manufacturing Practices (GMP) was promulgated. The GMP represents a quality assurance program intended to control the manufacturing, packaging, storage, distribution, and installation of medical devices. This regulation was intended to allow only safe and effective devices to reach the marketplace. It is this regulation that has had the greatest effect on the medical device industry. It allows the FDA to inspect a company's operations and take action on any noted deficiencies, including prohibition of device shipment.

In 1990, the Safe Medical Devices Act was passed by Congress. It gave the FDA authority to add "preproduction design validation controls" to the GMP regulations. The act also encouraged the FDA to work with foreign countries toward mutual recognition of GMP inspections.

On July 31, 1996, the new Medical Device Reporting (MDR) regulation became effective for user facilities and device manufacturers. The MDR regulation provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals are to detect and correct problems in a timely manner. Although the requirements of the regulation can be enforced through legal sanctions authorized by the FFD&C Act, the FDA relies on the goodwill and cooperation of all affected groups to accomplish the objectives of the regulation. The statutory authority for the MDR regulation is section 519 of the FFD&C Act, as amended by the Safe Medical Devices Act. The SMDA requires user facilities to

- Report device-related deaths to the FDA and the device manufacturer
- Report device-related serious injuries and serious illnesses to the manufacturer, or to the FDA, if the manufacturer is not known
- Submit to the FDA on a semiannual basis a summary of all reports submitted during that period

In 1990, the FDA proposed revised GMP regulations. Almost 7 years of debate and revision followed, but finally, on October 7, 1996, the FDA issued its final rules. The new Quality System Regulation, incorporating the required design controls, went into effect June 1, 1997. The design control provisions were not enforced until June 14, 1998.

16.2 DEVICE CLASSIFICATION

A medical device is any article or health care product intended for use in the diagnosis of disease or other condition or for use in the care, treatment, or prevention of disease that does not achieve any of its primary intended purposes by chemical action or by being metabolized (U.S. definition).

From 1962, when Congress passed the last major drug law revision and first attempted to include devices, until 1976, when device laws were finally written, there were almost constant congressional hearings. Testimony was presented by medical and surgical specialty groups, industry, basic biomedical sciences, and various government agencies, including the FDA. Nearly two dozen bills were rejected as either inadequate or inappropriate.

The Cooper Committee concluded that the many inherent and important differences between drugs and devices necessitated a regulatory plan specifically adapted to devices. They recognized that some degree of risk is inherent in the development of many devices, so that all hazards cannot be eliminated, that there is often little or no prior experience on which to base judgments about

safety and effectiveness, that devices undergo performance improvement modifications during the course of clinical trials, and that results also depend upon the skill of the user.

They therefore rejected the drug-based approach and created a new and different system for evaluating devices. All devices were placed into classes based upon the degree of risk posed by each individual device and its use. The premarket notification process (510[k]) and the Premarket Approval Application (PMAA) became the regulatory pathways for device approval. The investigational device exemption (IDE) became the mechanism to establish safety and efficacy in clinical studies for PMAAs.

16.2.1 Class I Devices

Class I devices are defined as non–life sustaining. Their failure poses no risk to life, and there is no need for performance standards. Basic standards, however, such as premarket notification (510[k]), registration, device listing, GMP, and proper record keeping are all required. Nonetheless, the FDA has exempted many of the simpler class I devices from some or all of these requirements. For example, tongue depressors and stethoscopes are both class I devices. Both are exempt from GMP; tongue depressors are exempt from 510(k) filing, whereas stethoscopes are not.

16.2.2 Class II Devices

Class II devices were also defined in 1976 as not life sustaining. However, they must not only comply with the basic standards for class I devices but also meet specific controls or performance standards. For example, sphygmomanometers, although not essential for life, must meet standards of accuracy and reproducibility.

Premarket notification is documentation submitted by a manufacturer that notifies the FDA that a device is about to be marketed. It assists the agency in making a determination about whether a device is "substantially equivalent" to a previously marketed predecessor device. As provided for in section 510(k) of the Food, Drug, and Cosmetic Act, the FDA can clear a device for marketing on the basis of premarket notification that the device is substantially equivalent to a pre-1976 predecessor device. The decision is based on premarket notification information that is provided by the manufacturer and includes the intended use, physical composition, and specifications of the device. Additional data usually submitted include in vitro and in vivo toxicity studies (as and if needed.)

The premarket notification or 510(k) process was designed to give manufacturers the opportunity to obtain rapid market approval of these noncritical devices by providing evidence that their device is "substantially equivalent" to a device that is already marketed. The device must have the same intended use and the same or equally safe and effective technological characteristics as a predicate device.

Class II devices are usually exempt from the need to prove safety and efficacy. The FDA, however, may require additional clinical or laboratory studies. On occasion, these may be as rigorous as for an IDE in support of a PMA (pre-market approval, to be discussed in Section 16.6.1), although this is rare. The FDA responds with an "order of concurrence" or nonconcurrence with the manufacturer's equivalency claims.

The Safe Medical Device Act of 1990 and the amendments of 1992 attempted to take advantage of what had been learned since 1976 to give both the FDA and manufacturers greater leeway by permitting reduction in the classification of many devices, including some life-supporting and life-sustaining devices previously in class III, provided that reasonable assurance of safety and effectiveness can be obtained by application of "special controls" such as performance standards, postmarket surveillance, guidelines, and patient and device registries.

16.2.3 Class III Devices

Class III devices were defined in 1976 as either sustaining or supporting life so that their failure is life threatening. For example, heart valves, pacemakers, and percutaneous transluminal coronary

angioplasty (PCTA) balloon catheters are all class III devices. Class III devices almost always require a PMAA, a long and complicated task fraught with many pitfalls that has caused the greatest confusion and dissatisfaction for both industry and the FDA.

The new regulations permit the FDA to use data contained in four prior PMAs for a specific device, which demonstrate safety and effectiveness, to approve future PMA applications by establishing performance standards or actual reclassification. Composition and manufacturing methods that companies wish to keep as proprietary secrets are excluded. Advisory medical panel review is now elective.

However, for PMAAs that continue to be required, all of the basic requirements for class I and II devices must be provided, plus failure mode analysis, animal tests, toxicology studies, and then, finally, human clinical studies, directed to establish safety and efficacy under an IDE.

It is necessary that preparation of the PMA must actually begin years before it will be submitted. It is only after the company has the results of all of the laboratory testing, preclinical animal testing, failure mode analysis, and manufacturing standards on their final design that their proof of safety and efficacy can begin, in the form of a clinical study under an IDE.

At this point, the manufacturer must not only have settled on a specific, fixed design for his device, but with his/her marketing and clinical consultants, must also have decided on what the indications, contraindications, and warnings for use will be. The clinical study must be carefully designed to support these claims.

Section 520(g) of the FFD&C Act, as amended, authorizes the FDA to grant an IDE to a researcher using a device in studies undertaken to develop safety and effectiveness data for that device when such studies involve human subjects. An approved IDE application permits a device that would otherwise be subject to marketing clearance to be shipped lawfully for the purpose of conducting a clinical study. An approved IDE also exempts a device from certain sections of the act. All new significant risk devices not granted substantial equivalence under the 510(k) section of the act must pursue clinical testing under an IDE.

It is worth noting that the FDA may, with justifications such as adverse event reporting, require that a previously rated class II device be redesignated as a class III device, with the attendant retesting of the entire process. Such a reclassification was proposed in 2013 for metal-on-metal hip prostheses.

An institutional review board (IRB) is a group of physicians and lay people at a hospital who must approve clinical research projects prior to their initiation (see Section 16.7.1 for additional explanations). These projects include device, drug, combination, and process studies.

16.3 REGISTRATION AND LISTING

Under section 510 of the act, every person engaged in the manufacture, preparation, propagation, compounding, or processing of a device shall register their name, place of business, and such establishment. This includes manufacturers of devices and components, repackers, and relabelers, as well as initial distributors of imported devices. Those not required to register include manufacturers of raw materials, licensed practitioners, manufacturers of devices for use solely in research or teaching, warehouses, manufacturers of veterinary devices, and those who only dispense devices, such as pharmacies.

Upon registration, the FDA issues a device registration number. A change in the ownership or corporate structure of the firm, the location, or person designated as the official correspondent must be communicated to the FDA device registration and listing branch within 30 days. Registration must be done when first beginning to manufacture medical devices and must be updated yearly.

Section 510 of the act also requires all manufacturers to list the medical devices they market. Listing must be done when first beginning to manufacture a product and must be updated every 6 months. Listing includes not only informing the FDA of products manufactured but also providing the agency with copies of labeling and advertising.

Foreign firms that market products in the United States are permitted but not required to register and are required to list. Foreign devices that are not listed are not permitted to enter the country.

Registration and listing provides the FDA with information about the identity of manufacturers and the products they make. This information enables the agency to schedule inspections of facilities and also to follow up on problems. When the FDA learns about a safety defect in a particular type of device, it can use the listing information to notify all manufacturers of those devices about that defect.

16.4 THE 510(k) PROCESS

16.4.1 Determining Substantial Equivalency

A new device is substantially equivalent if, in comparison to a legally marketed predicate device, it has the same intended use and (1) has the same technological characteristics as the predicate device or (2) has different technological characteristics and submitted information that does not raise different questions of safety and efficacy and demonstrates that the device is as safe and effective as the legally marketed predicate device. Figure 16.1 is an overview of the substantial equivalence decision-making process.

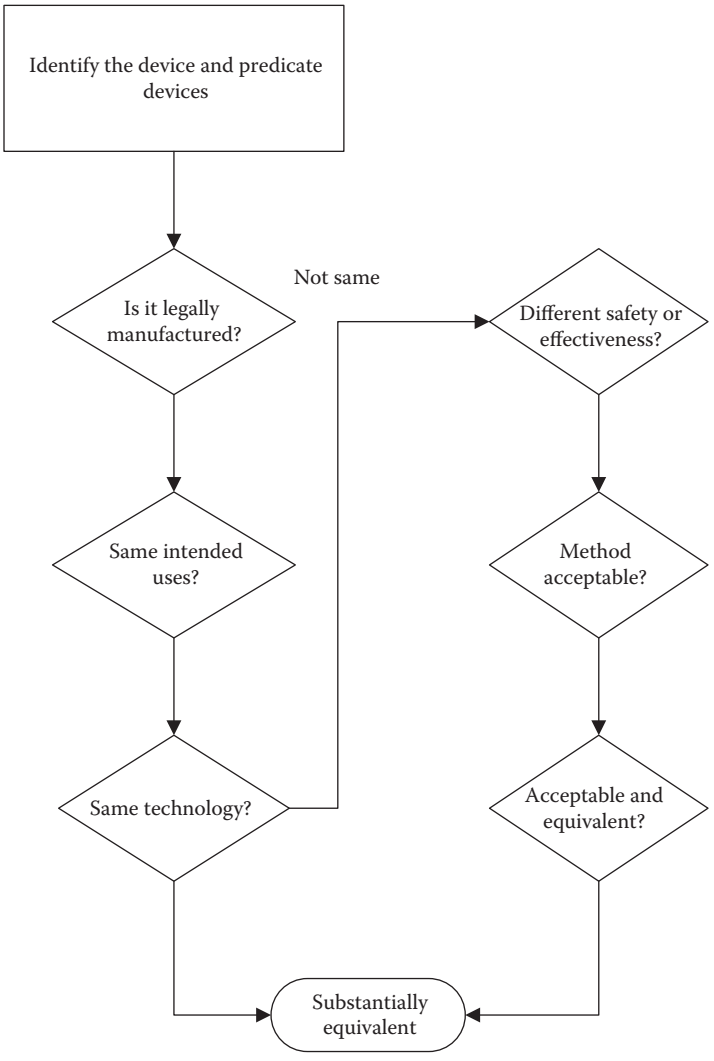

FIGURE 16.1 Substantial equivalence decision-making process.

16.4.2 The Regular 510(k)

16.4.2.1 Types of 510(k)s

There are several types of 510(k) submissions that require different formats for addressing the requirements. These include the following:

- Submissions for identical devices
- Submissions for equivalent but not identical devices
- Submissions for complex devices or for major differences in technological characteristics
- Submissions for software-controlled devices

The 510(k) for simple changes or for identical devices should be kept simple and straightforward. The submission should refer to one or more predicate devices. It should contain samples of labeling, it should have a brief statement of equivalence, and it may be useful to include a chart listing similarities and differences.

The group of equivalent but not identical devices includes combination devices where the characteristics or functions of more than one predicate device are relied on to support a substantially equivalent determination. This type of 510(k) should contain all of the information listed here as well as sufficient data to demonstrate why the differing characteristics or functions do not affect safety or effectiveness. Submission of some functional data may be necessary. It should not be necessary, however, to include clinical data—bench or preclinical testing results should be sufficient. Preparing a comparative chart showing differences and similarities with predicate devices can be particularly helpful to the success of this type of application.

Submissions for complex devices or for major differences in technological characteristics is the most difficult type of submission, since it begins to approach the point at which the FDA will need to consider whether a 510(k) is sufficient or whether a PMAA must be submitted. The key is to demonstrate that the new features or the new uses do not diminish safety or effectiveness and that there are no significant new risks posed by the device. In addition to the types of information described previously, this type of submission will almost always require submission of some data, possibly including clinical data.

As a general rule, it often is a good idea to meet with the FDA to explain why the product is substantially equivalent, to discuss the data that will be submitted in support of a claim of substantial equivalence, and to learn the FDA's concerns and questions so that these may be addressed in the submission. The FDA's guidance documents can be of greatest use in preparing this type of submission.

The term *software* includes programs and or data that pertain to the operation of a computer-controlled system, whether they are contained on memory sticks, hard disks, CDs, or DVDs, or embedded in the hardware of a device. The depth of review by the FDA is determined by the "level of concern" for the device and the role that the software plays in the functioning of the device. Levels of concern are listed as minor, moderate, and major and are tied very closely with risk analysis.

In reviewing such submissions, the FDA maintains that end product testing may not be sufficient to establish that the device is substantially equivalent to the predicate devices. Therefore, a firm's software development process and/or documentation should be examined for reasonable assurance of safety and effectiveness of the software-controlled functions, including incorporated safeguards. 510(k)s that are heavily software dependent will receive greater FDA scrutiny, and the questions posed must be satisfactorily addressed.

16.4.2.2 The 510(k) Format

The actual 510(k) submission will vary in complexity and length according to the type of device or product change for which substantial equivalency is sought. (See FDA website for "guidance

documents.") A submission shall be in sufficient detail to provide an understanding of the basis for a determination of substantial equivalence. All submissions shall contain the following information:

- The submitter's name, address, and telephone number; a contact person; and the date the submission was prepared.
- The name of the device, including the trade or proprietary name, if applicable, the common or usual name, and the classification name.
- An identification of the predicate or legally marketed device or devices to which substantial equivalence is being claimed.
- A description of the device that is the subject of the submission, including an explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device such as device design, materials used, and physical properties.
- A statement of the intended use of the device, including a general description of the diseases or conditions the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is intended. If the indication statements are different from those of the predicate or legally marketed device identified previously, the submission shall contain an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device and why the differences do not affect the safety or effectiveness of the device when used as labeled.
- A statement of how the technological characteristics (design, material, chemical composition, or energy source) of the device compare to those of the predicate or legally marketed device identified previously.

510(k) summaries for those premarket notification submissions in which a determination of substantial equivalence is based on an assessment of performance data shall contain the following information in addition to that listed previously:

- A brief discussion of the nonclinical tests and their results submitted in the premarket notification.
- A brief discussion of the clinical tests submitted, referenced, or relied on in the premarket notification submission for a determination of substantial equivalence. This discussion shall include, where applicable, a description of the subjects upon whom the device was tested, a discussion of the safety and/or effectiveness data obtained with specific reference to adverse effects and complications, and any other information from the clinical testing relevant to a determination of substantial equivalence.
- The conclusions drawn from the nonclinical and clinical tests that demonstrate that the device is safe and effective and performs as well as or better than the legally marketed device identified previously.

The summary should be in a separate section of the submission, beginning on a new page and ending on a page not shared with any other section of the premarket notification submission, and should be clearly identified as a 501(k) summary.

A 510(k) statement submitted as part of a premarket notification shall state as follows:

> I certify that (name of person required to submit the premarket notification) will make available all information included in this premarket notification on safety and effectiveness that supports a finding of substantial equivalence within 30 days of request by any person. The information I agree to make available does not include confidential patient identifiers.

This statement should be made in a separate section of the premarket notification submission and should be clearly identified as a 510(k) statement.

A class III certification submitted as part of a premarket notification shall state as follows:

> I certify that a reasonable search of all information known or otherwise available to (name of premarket notification submitter) about the types and causes of reported safety and/or effectiveness problems for the (type of device) has been conducted. I further certify that the types of problems to which the (type of device) is susceptible and their potential causes are listed in the attached class III summary, and that this class III summary is complete and accurate.

This statement should be clearly identified as a class III certification and should be made in the section of the premarket notification submission that includes the class III summary.

A 510(k) should be accompanied by a brief cover letter that clearly identifies the submission as a 510(k) premarket notification. To facilitate prompt routing of the submission to the correct reviewing division within the FDA, the letter can mention the generic category of the product and its intended use.

When the FDA receives a 510(k) premarket notification, it is reviewed according to a checklist to ensure its completeness. A sample 510(k) checklist is shown in Table 16.1. This is the outline form of the checklist in 2012; a newer, longer version was proposed in 2012.

16.4.3 The Special 510(k)

Under this option, a manufacturer who is intending to modify their own legally marketed device will conduct the risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements. Once the manufacturer has ensured the satisfactory completion of this process, a *Special 510(k): Device Modification* may be submitted. While the basic content requirements of the 510(k) will remain the same, this type of submission should also reference the cleared 510(k) number and contain a *Declaration of Conformity* with design control requirements.

Under the Quality System Regulation, manufacturers are responsible for performing internal audits to assess their conformance with design controls. A manufacturer could, however, use a third party to provide a supporting assessment of the conformance. In this case, the third party will perform a conformance assessment for the device manufacturer and provide the manufacturer with a statement to this effect. The marketing application should then include a Declaration of Conformity signed by the manufacturer, while the statement from the third party should be maintained in the device master record. As always, responsibility for conformance with design control requirements rests with the manufacturer.

In order to provide an incentive for manufacturers to choose this option, the Office of Device Evaluation (ODE) intends to process Special 510(k)s within 30 days of receipt by the document mail center. The Special 510(k) option will allow the agency to review modifications that do not affect the device's intended use or alter the device's fundamental scientific technology within this abbreviated time frame. The agency believes that modifications that affect the intended use or alter the fundamental scientific technology of the device are not appropriate for review under this type of application, but rather, should continue to be subject to the traditional 510(k) procedures.

To ensure the success of the Special 510(k) option, there must be a common understanding of the types of device modifications that may gain marketing clearance by this path. Therefore, it is critical that industry and FDA staff can easily determine whether a modification is appropriate for submission by this option. To optimize the chance that this option will be accepted and promptly cleared, manufacturers should evaluate each modification against the considerations described as follows to ensure that the particular change does not

- Affect the intended use
- Alter the fundamental scientific technology of the device

16.4.3.1 Special 510(k) Content

A Special 510(k) should include the following:

- A cover sheet clearly identifying the application as a "Special 510(k): Device Modification"
- The name of the legally marketed (unmodified) device and the 510(k) number under which it was cleared
- Item required under paragraph 807.87, including a description of the modified device and a comparison to the cleared device, the intended use of the device, and the proposed labeling for the device
- A concise summary of the design control activities, including (1) an identification of the risk analysis method(s) used to assess the impact of the modification on the device and its components as well as the results of the analysis, (2) based on the risk analysis, an identification of the verification and/or validation activities required, including methods or tests used and the acceptance criteria applied, and (3) a Declaration of Conformity with design controls

The Declaration of Conformity should include the following:

- A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met
- A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review

These two statements should be signed by the designated individual(s) responsible for those particular activities.

16.4.4 The Abbreviated 510(k)

Device manufacturers may choose to submit an Abbreviated 510(k) when

- A guidance document exists
- A special control has been established
- The FDA has recognized a relevant consensus standard

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87. In addition, manufacturers submitting an Abbreviated 510(k) that relies on a guidance document and/or special control(s) should include a summary report that describes how the guidance document and/or special control(s) were used during device development and testing. The summary report should include information regarding the manufacturer efforts to conform with the guidance document and/or special control(s) and should outline any deviations. Persons submitting an Abbreviated 510(k) that relies on a recognized standard should provide the information described as follows (except for the summary report) and a Declaration of Conformity to the recognized standard.

In an Abbreviated 510(k), a manufacturer will also have the option of using a third party to assess conformance with the recognized standard. Under this scenario, the third party will perform a conformance assessment to the standard for the device manufacturer and should provide the manufacturer with a statement to this effect. Like a Special 510(k), the marketing application should

TABLE 16.1
Sample 510(k) Checklist

	Critical Elements	Yes	No
1	Is the product a device?		
2	Is the device exempt from 510(k) by regulation or policy?		
3	Is the device subject to review by Center for Devices and Radiological Health (CDRH)?		
4	Are you aware that this device has been the subject of a previous decision of not substantially equivalent (NSE)? If yes, does this new 510(k) address the NSE issues?		
5	Are you aware of the submitter being the subject of an integrity investigation? If yes, consult the Office of Device Evaluation (ODE) integrity officer.		
6	Has the ODE integrity officer given permission to proceed with the review? (Blue Book Memo #191-2 and *Federal Register* 90N-0332, September 10, 1990.)		
7	Does the submission contain the information required under Sections 510(k), 513(f), and 513(I) of the FFD&C Act and Subpart E of part 807 in title 21 of the *Code of Federal Regulations* (CFR)?		
8	Device trade or proprietary name?		
9	Device common or usual name or classification name?		
10	Establishment registration number? (Only applies if the establishment is registered.)		
11	Class into which the device is classified under 21 CFR parts 862–892?		
12	Classification panel?		
13	Action taken to comply with Section 514 of the act?		
14	Proposed labels, labeling, and advertisements (if available) that describe the device, its intended use, and directions for use? (Blue Book Memo #G91-1.)		
15	A 510(k) summary of safety and effectiveness or a 510(k) statement that safety and effectiveness information will be made available to any person upon request?		
16	For class III devices only, a class III certification and a class III summary?		
17	Photographs of the device?		
18	Engineering drawings for the device with dimensions and tolerances?		
19	The marketed device(s) to which equivalence is being claimed including labeling and description of the device?		
20	Statement of similarities and/or differences with marketed devices?		
21	Data to show consequences and effects of a modified device(s)?		
22	Additional information that is necessary under 21 CFR 807.87 (h)?		
23	Submitter's name and address?		
24	Contact person, telephone number, and fax number?		
25	Representative/consultant, if applicable?		
26	Table of contents, with pagination?		
27	Address of manufacturing facility/facilities and, if appropriate, sterilization site(s)?		
28	Additional information that may be necessary under 21 CFR 807.87 (h)?		
29	Comparison table of the new device to the marketed device?		
30	Action taken to comply with voluntary standards?		
31	Performance data:		
	Marketed device?		
	Bench testing?		
	Animal testing?		
	Clinical data?		
	New device?		
	Bench testing?		
	Animal testing?		
	Clinical data?		
32	Sterilization information?		

(*continued*)

TABLE 16.1 (Continued)
Sample 510(k) Checklist

	Critical Elements	Yes	No
33	Software information?		
34	Hardware information?		
35	Is this 510(k) for a kit; has the kit certification statement been provided?		
36	Is this device subject to issues that have been addressed in specific guidance document(s)? If yes, continue review with checklist from any appropriate guidance document. If no, is 510(k) sufficiently complete to allow substantive review?		
37	Truthfulness certification?		
38	Other as required?		

include a Declaration of Conformity signed by the manufacturer, while the statement from the third party should be maintained in the device master record pursuant to the Quality System Regulation. Responsibility for conformance with the recognized standard, however, rests with the manufacturer, not the third party.

The incentive for manufacturers to elect to provide summary reports on the use of guidance documents and/or special controls or declarations of conformity to recognized standards will be an expedited review of their submissions. While abbreviated submissions will compete with traditional 510(k) submissions, it is anticipated that their review will be more efficient than that of traditional 510(k) submissions, which tend to be data intensive. In addition, by allowing ODE reviewers to rely on a manufacturer's summary report on the use of a guidance document and/or special controls and declarations of conformity with recognized standards, review resources can be directed at more complicated issues, and thus, this should expedite the process.

16.4.4.1 Abbreviated 510(k) Content

An Abbreviated 510(k) should include the following:

- A cover sheet clearly identifying the application as an Abbreviated 510(k)
- Items required under paragraph 21 CFR 807.87, including a description of the device, the intended use of the device, and the proposed labeling for the device
- For a submission that relies on a guidance document and/or special control(s) documentation regarding what methods were used to address the risks associated with the particular device type
- For a submission that relies on a recognized standard, a Declaration of Conformity to the standard data/information to address issues not covered by guidance documents, special controls, and/or recognized standards
- Indications for use enclosure
- Labelling and advertisement materials

16.5 DECLARATION OF CONFORMANCE TO A RECOGNIZED STANDARD

Declarations of conformity to recognized standards should include the following information:

- An identification of the applicable recognized consensus standards that were met
- A specification, for each consensus standard, that all requirements were met, except for inapplicable requirements or deviations noted here

- An identification for each consensus standard, of any manner(s) in which the standard may have been adopted for application to the device under review (e.g., an identification of an alternative series of tests that were performed)
- An identification for each consensus standard of any requirements that were not applicable to the device
- A specification of any deviations from each applicable standard that were applied
- A specification of the differences that may exist, if any, between the tested device and the device to be marketed and a justification of the test results in these areas of difference
- The name and address of any test laboratory or certification body involved in determining the conformance of the device with the applicable consensus standards and a reference to any accreditations of those organizations

16.6 THE PMA APPLICATION

PMA is an approval application for a class III medical device, including all information submitted with or incorporated by reference. The purpose of the regulation is to establish an efficient and thorough device review process to facilitate the approval of PMAs for devices that have been shown to be safe and effective for their intended use and that otherwise meet the statutory criteria for approval, while ensuring the disapproval of PMAs for devices that have not been shown to be safe and effective or that do not otherwise meet the statutory criteria for approval.

16.6.1 The PMA Process

The first step in the PMAA process is the filing of the IDE application for significant-risk devices. The IDE is reviewed by the FDA, and once accepted, the sponsor can proceed with clinical trials.

16.6.2 Contents of a PMAA

Section 814.20 of 21 CFR defines what must be included in an application, including the following:

- Name and address
- Application procedures and table of contents
- Summary
- Complete device description
- Reference to performance standards
- Nonclinical and clinical investigations
- Justification for single investigator
- Bibliography
- Sample of device
- Proposed labeling
- Environmental assessment
- Other information

The summary should include indications for use, a device description, a description of alternative practices and procedures, a brief description of the marketing history, and a summary of studies. This summary should be of sufficient detail to enable the reader to gain a general understanding of the application. The PMAA must also include the applicant's foreign and domestic marketing history as well as any marketing history of a third party marketing the same product.

The description of the device should include a complete description of the device, including pictorial presentations. Each of the functional components or ingredients should be described, as

well as the properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition. The principles of the device's operation should also be explained. Information regarding the methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and installation of the device should be explained in sufficient detail so that a person generally familiar with current GMP can make a knowledgeable judgment about the quality control used in the manufacture of the device.

To clarify which performance standards must be addressed, applicants may ask members of the appropriate reviewing division of the ODE or consult the FDA's list of relevant voluntary standards or the Medical Device Standards Activities Report.

16.7 IDE

The purpose of the IDE regulation is to encourage the discovery and development of useful devices intended for human use while protecting public health. It provides the procedures for the conduct of clinical investigations of devices. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with a performance standard or having marketing clearance.

16.7.1 IRBs

Any human research covered by federal regulation will not be funded unless it has been reviewed by an IRB. The fundamental purpose of an IRB is to ensure that research activities are conducted in an ethical and legal manner. Specifically, IRBs are expected to ensure that each of the basic elements of informed consent, as defined by regulation, are included in the document presented to the research participant for signature or verbal approval.

The deliberations of the IRB must determine the following:

- The risks to subjects are equitable.
- The selection of subjects is equitable.
- Informed consent will be sought from each prospective subject or his/her legally authorized representative.
- Informed consent will be appropriately documented.
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to assure the safety of the subjects.
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

It is axiomatic that the IRB should ensure that the risks of participation in a research study should be minimized. The IRB must determine that this objective is to be achieved by ensuring that investigators use procedures that are consistent with sound research design and that do not necessarily expose subjects to excessive risk. In addition, the IRB needs to assure that the investigators, whenever appropriate, minimize risk and discomfort to the research participants by using, where possible, procedures already performed on the subjects as part of routine diagnosis or treatment.

The IRB is any board, committee, or other group formally designated by an institution to review, to approve the initiation of and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of human subjects.

An IRB must comply with all applicable requirements of the IRB regulation and the IDE regulation in reviewing and approving device investigations involving human testing. An IRB has the authority to review and approve, require modification of, or disapprove an investigation. If no IRB

exists or if the FDA finds an IRB's review to be inadequate, a sponsor may submit an application directly to the FDA.

An investigator is responsible for the following:

- Ensuring that the investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations
- Protecting the rights, safety, and welfare of subjects
- Control of the devices under investigation

An investigator is also responsible for obtaining informed consent and maintaining and making reports.

16.7.2 IDE Format

There is no preprinted form for an IDE application, but the following information must be included in an IDE application for a significant-risk device investigation. Generally, an IDE application should contain the following:

- Name and address of sponsor
- A complete report of prior investigations
- A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device
- An example of the agreements to be signed by the investigators and a list of the names and addresses of all investigators
- Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study
- A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation
- The name and address of any institution (other than those listed previously) where a part of the investigation may be conducted
- The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization
- A claim for categorical exclusion or an environmental assessment
- Copies of all labeling for device
- Copies of all informed consent forms and all related information materials provided to subjects
- Any other relevant information that FDA requests for review of the IDE application

16.8 GOOD LABORATORY PRACTICES

In 1978, the FDA adopted Good Laboratory Practices (GLP) rules and implemented a laboratory audit and inspection procedure covering every regulated entity that conducts nonclinical laboratory studies for product safety and effectiveness. The GLPs were amended in 1984.

The GLP standard addresses all areas of laboratory operations, including requirements for a quality assurance unit to conduct periodic internal inspections and keep records for audit and reporting purposes, standard operating procedures (SOPs) for all aspects of each study and for all phases of laboratory maintenance, a formal mechanism for evaluation and approval of study protocols and their amendments, and reports of data in sufficient detail to support conclusions drawn from them.

The FDA inspection program includes GLP compliance and a data audit to verify that information submitted to the agency accurately reflects the raw data.

16.9 GMP

The FDA is authorized, under section 520(f) of the act, to promulgate regulations detailing compliance with current GMPs. GMPs include the methods used in, and the facilities and controls used for, the manufacture, packing, storage, and installation of a device. The GMP regulations were established as manufacturing safeguards to ensure the production of a safe and effective device and include all of the essential elements of a quality assurance program. Because manufacturers cannot test every device, the GMPs were established as a minimum standard of manufacturing to ensure that each device produced would be safe. If a product is not manufactured according to GMPs, even if it is later shown not to be a health risk, it is in violation of the act and subject to FDA enforcement action.

The general objectives of the GMPs, not specific manufacturing methods, are found in part 820 of the *Code of Federal Regulations*. The GMPs apply to the manufacture of every medical device. The newest GMP regulations were released in 1996 and gave the FDA the authority to examine the design area of the product development cycle for the first time. The regulation also parallels very closely the ISO 9000 set of standards.

16.10 HUMAN FACTORS

In April 1996, the FDA issued a draft primer on the use of human factors in medical device design, entitled *Do It by Design*. The purpose of the document was to improve the safety of medical devices by minimizing the likelihood of user error by systematic, careful design of the user interface, that is, the hardware and software features that define the interaction between the users and the equipment. The document contains background information about human factors as a discipline, descriptions and illustrations of device problems, and a discussion of human factors methods. It also contains recommendations for manufacturers and health facilities.

As the source for this document, the FDA extensively used the guideline *Human Factors Engineering Guidelines and Preferred Practices for the Design of Medical Devices* published by the Association for the Advancement of Medical Instrumentation as well as interfaced with human factors consultants. It is expected that human factors requirements will become part of the product submission as well as the GMP inspection. It is cited in most updates to, for example, 510(k) guidelines. It is a document worth reviewing by the readers of this text.

16.11 DESIGN CONTROL

With the publication of the new GMP regulations, the FDA has the authority to cover design controls in their inspections. The FDA issued a draft guidance document in March 1996 entitled *Design Control Guidance for Medical Device Manufacturers*. The final document was published in March 1997. The purpose of the document was to provide readers with an understanding of what is meant by "control" in the context of the requirements. By providing an understanding of what constitutes control of a design process, readers could determine how to apply the concepts in a way that was both consistent with the requirements and best suited for their particular situation.

Three underlying concepts served as a foundation for the development of this guidance:

- The nature of the application of design controls for any device should be proportional to both the complexity of and the risks associated with that device.

- The design process is a multifunctional one that involves other departments besides design and development if it is to work properly, thus involving senior management as an active participant in the process.
- The product life cycle concept serves throughout the document as the framework for introducing and describing the design control activities and techniques.

Design control concepts are applicable to process development as well as product development. The extent is dependent upon the nature of the product and processes used to manufacture the product. The safety and performance of a new product are also dependent on an intimate relationship between product design robustness and process capability.

The document covers the following areas:

- Risk management
- Design and development planning
- Organizational and technical interfaces
- Design input
- Design output
- Design review
- Design verification
- Design validation
- Design changes
- Design transfer

These topics are covered in detail in Sections 16.3 through 16.6.

16.12 THE FDA AND SOFTWARE

The subject of software in and as a medical device has become an important topic for the FDA. This interest began in 1985, when software in a radiation treatment therapy device is alleged to have resulted in a lethal overdose. The FDA then analyzed recalls by fiscal year (FY) to determine how many were caused by software problems. In FY 1985, for example, 20% of all neurology device recalls were attributable to software problems, while 8% of cardiovascular problems had the same cause. This type of analysis, along with the results of various corporate inspections, led the FDA to conclude that some type of regulation was required.

Since there are many types of software in use in the medical arena, the problem of the best way to regulate it has become an issue for the FDA. Discussions have centered on what type of software is a medical device, the type of regulation required for such software, and what could be inspected under current regulations. Agency concerns fall into three major categories: medical device software, software used in manufacturing, and software information systems used for clinical decision making.

For medical device software, the FDA is responsible for assuring that the device utilizing the software is safe and effective. It only takes a few alleged serious injuries or deaths to sensitize the agency to a particular product or generic component that deserves attention. The agency's review of MDR incidents and analysis of product recalls has convinced the agency that software is a factor contributing to practical problems within devices.

When software is used during manufacturing, the FDA is concerned with whether or not the software controlling a tool or automatic tester is performing as expected. The FDA's perceptions are rooted in experiences with GMP inspections of pharmaceutical manufacturers, where computers are heavily depended upon for control of manufacturing processes. Although there are few incidents of device or manufacturing problems traceable to flaws in manufacturing software, GMP inspections have focused intensively on validation of software programs used in industry for control of manufacturing operations.

With regard to stand-alone software used to aid clinical decision making, the FDA is concerned with hypothetical problems rather than extensive records of adverse incidents. While most commercially available health care information systems replace manual systems that had a far higher potential for error, the FDA believes that regulations should apply to the kinds of systems that may influence clinical treatment or diagnoses. The FDA has observed academic work of "expert systems" used by medical professionals and is concerned that such systems may be commercialized without sufficient controls.

The FDA has published guidelines for developing quality software, off-the-shelf software, the requirements for product approval submissions (510[k]), and the inspection of software-controlled test fixtures as a part of GMP inspections. They have also conducted training courses for their inspectors and submission reviewers on the subject of software and computer basics.

16.13 SOFTWARE CLASSIFICATION

When a computer product is a component, part, or accessory of a product recognized as a medical device in its own right, the computer component is regulated according to the requirements for the parent device unless the component of the device is separately classified. Computer products that are medical devices and not components, parts, or accessories of other products that are themselves medical devices are subject to one of three degrees of regulatory control depending on their characteristics. These products are regulated with the least degree of control necessary to provide reasonable assurance of safety and effectiveness. Computer products that are substantially equivalent to a device previously classified will be regulated to the same degree as the equivalent device. Those devices that are not substantially equivalent to a preamendment device or that are substantially equivalent to a class III device are regulated as class III devices.

Medical software is divided into three classes, with regulatory requirements specific to each:

- Class I software is subject to the act's general controls relating to such matters as misbranding, registration of manufacturers, record keeping, and GMPs. An example of class I software would be a program that calculates the composition of infant formula.
- Class II software is that for which general controls are insufficient to provide reasonable assurance of safety and effectiveness and for which performance standards can provide assurance. This is exemplified by a computer program designed to produce radiation therapy treatment plans.
- Class III software is that for which insufficient information exists to assure that general controls and performance standards will provide reasonable assurance of safety and effectiveness. Generally, these devices are represented to be life sustaining or life supporting and may be intended for a use that is of substantial importance in preventing impairment to health. They may be implanted in the body or present a potential unreasonable risk of illness or injury. A program that measures glucose levels and calculates and dispenses insulin based upon those calculations without physician intervention would be a class III device.

16.14 THE FDA INSPECTION

The FDA's power to inspect originates in Section 704 of the FFD&C Act. This provision allows FDA officials to inspect any factory, warehouse, or establishment in which devices are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction. In addition to the "establishments" specification, the FDA is permitted to enter any vehicle used to transport or hold regulated products for export or in interstate commerce. The inspection power is specifically extended to medical device manufacturers by Sections 519 and 520 of the FFD&C Act.

Every FDA inspector is authorized by law to inspect all equipment that is used in the manufacturing process. Furthermore, investigators may examine finished and unfinished devices and device components, containers, labeling for regulated products, and all documents that are required to be kept by the regulations, such as device master records and device history records.

Despite the broad inspectional authority over restricted devices, the statute provides that regardless of the device's unrestricted status, certain information is excluded from the FDA's inspectional gambit. The kind of information to which the FDA does not have access includes financial data, sales data, and pricing data. The new GMPs give the FDA authority to inspect the design area and the qualifications of personnel in all aspects of the product development process.

16.15 ADVICE ON DEALING WITH THE FDA

Several recommendations can be made regarding how to deal with the FDA and its regulatory process. None of these bits of advice are dramatic or new, but in the course of observing a firm's interaction with the agency, it is amazing how many times the failure to think of these steps can result in significant difficulties.

Know your district office. This may not be an easy thing to accomplish, since, understandably, there is a great reluctance to walk into a regulatory agency and indicate you are there to get acquainted. As opportunities arise, however, they should not be overlooked. Situations such as responding to a notice of an investigator's observations at the conclusion of an inspection or a notice of adverse findings letter are excellent opportunities to hand deliver a reply instead of simply mailing it. The verbal discussion with the reply may make the content much more meaningful and will allow both sides to learn more about the intent and seriousness with which the subject is being approached.

Prepare for inspections. When the FDA investigator walks into your manufacturing facility or corporate offices, there should be a procedure established that everyone is familiar with as to who is called, who escorts the investigator through the facility, who is available to make copies of records requested, and so forth. A corollary to this suggestion is to be prepared to deal with adverse inspectional findings or other communications from the agency that indicate that the FDA has found violations, a serious health hazard, or other information that requires high-level company knowledge and decision making.

Take seriously 483s and letters. Many regulatory actions are processed with no apparent indication that a firm seriously considered the violations noted by the agency.

Keep up with current events and procedures of the FDA. This will minimize the changes or surprise interpretations that could have an effect on a firm's operations and will allow for advance planning for new FDA requirements. The agency publishes much of its new program information in bulletins and other broad-distribution documents, but much more can be learned from obtaining copies of FDA Compliance Policy Guides and Compliance Programs.

Let the FDA know of your firm's opinions on issues, whether they are in the development state at the agency or are policies or programs established and in operation. The agency does recognize that the firms it regulates are the true experts in device manufacturing and distribution, and their views are important. The agency also recognizes that the regulation of manufacturers is not the only bottom line—solving public health problems is equally or more important, and there are generally many ways to solve those problems.

EXERCISES

1. The meat industry is, despite efforts since 1906, still a major concern for some individuals. Find and discuss any recently reported hamburger spoilage problem.
2. Feedback mechanisms are of value in electronic and mechanical control systems. Why are they not useful for material flows, such as foodstuffs?

3. Perform a web search for patent medicines; document two interesting examples.
4. Why did the FDA not have intrastate control in 1906?
5. Find, using the FDA website, any warning letter of interest to you and report on it.
6. Use the MAUDE database to do a search for device = bed, outcome = death, for any recent year. Report on your results.
7. Select a medical device used by one of your acquaintances; do a MAUDE search to determine if there have been any negative outcomes in the past 5 years.
8. Perform a web search for quack medical devices. Report on one.
9. Much recent television advertising exaggerates claims for nonmedical drugs or devices (such as "Viagra" and muscle stimulators). Find and report on an example; discuss how "truth" is being "bent." What would it take to get the FDA involved?

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17 Food and Drug Administration History and Relevant Nondevice Regulations

The Food and Drug Administration (FDA) in the United States is currently responsible for regulations and enforcement actions for food, drugs, medical devices, radiation-emitting products, vaccines, blood and biologics, animal and veterinary medicine equivalents, cosmetics, and recently, tobacco products. Chapter 16 covered the FDA's responsibility primarily in the area of medical devices such as a biomedical engineer might be responsible for designing and building and testing. This chapter will cover some of the relevant material, again for biomedical engineers, in terms of drug development and testing, veterinary drugs, cosmetics, and dual-use products—which are combinations of drugs and devices. We will begin the chapter with a bit of history in order to better justify the powers of the FDA and how they have evolved over the last 100+ years of existence.

17.1 A BRIEF HISTORY OF THE FDA RELEVANT TO FOOD AND DRUGS

The first pharmacopeia in U.S. literature was developed in 1820 (http://www.fda.gov/aboutfda/whatwedo/history/milestones/ucm128305.htm). A pharmacopoeia is a formal listing of all recognized drugs in use at the time. It has been updated on a regular basis and remains the standard in terms of U.S. laws and regulations at the current time. The first major drug regulation was passed by Congress in 1848 and was termed the drug importation act. Its purpose was to stop the import of adulterated drugs from overseas. With the pharmacopeia in place, Congress had the definition as to what constituted a drug and the expected results of using that drug. At the time, and to a lesser extent now, adulteration of drugs was a problem. Adulteration is the act of cutting, for example, a drug, with a thinning agent such as alcohol in order to sell a larger quantity of the "original" material. Adulteration can also involve food supplies and, at the time, could, for example, involve the addition of coloring and other agents to mask the taste and odor of spoiled foods. Adulteration in foods can be safe, such as adding sugar water to honey or distilled water to whiskey, but it is not necessarily legal. It can also be unsafe. For example, lead "tastes" sweet and can and has been used as a sweetener and colorant. Food and drug adulteration were safety concerns throughout the 1800s.

In 1862, President Lincoln appointed a chemist as the first head of a newly authorized Department of Agriculture. Over a period of years, the Bureau of Chemistry evolved within it; this unit later became the FDA. Beginning in 1880 and continuing for 25 years, the first of a series of 100 food and drug bills were introduced into Congress. An FDA law was first proposed in 1880. Food adulteration studies were a concern for many in the Bureau of Chemistry during this time interval. In 1883, Dr. Harvey W. Wiley became chief chemist, expanding the Bureau of Chemistry's food adulteration studies. Campaigning for a federal law, Dr. Wiley was called the "Crusading Chemist" and "Father of the Pure Food and Drugs Act." In 1898, the Association of Official Agricultural Chemists established a Committee on Food Standards headed by Dr. Wiley, and states began incorporating these standards into their food statutes. In 1902, the Biologics Control Act was passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans. In addition, Congress authorized the Bureau of Chemistry to study chemical preservatives and colors

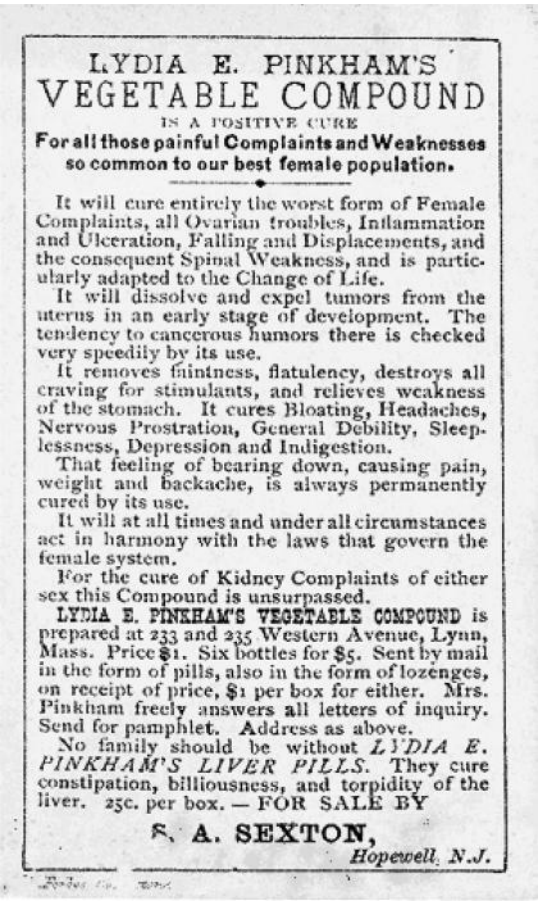
and their effects on digestion and health. Dr. Wiley's published studies drew widespread attention to the problem of food adulteration. Progress was slow via this legislative method; it took public outrage to force the forming of the then-nascent FDA.

Two major items in the eyes of this author helped instigate the government to first form the FDA. The first item involved studies of the drugs that were commonly advertised as nostrums (http://www.mc.vanderbilt.edu/biolib/hc/nostrums/cards.html). The second, to be discussed shortly, was due to publicity regarding meat production.

A nostrum is defined as a medicine of secret composition recommended by its preparer but usually without scientific proof of its effectiveness (http://www.merriam-webster.com/dictionary/nostrum). Several were heavily advertised via advertising cards in the late 1800s and into the very early 1900s. One popular nostrum, for example, was "Lydia E. Pinkham's Vegetable Compound" (see Figures 17.1 and 17.2), which advertised in part that "it will cure entirely the worst form of female complaints, all ovarian troubles, inflammation and ulceration, falling and displacements, and is particularly adapted to the change of life" and "for the cure of kidney complaints of either sex this compound is unsurpassed." This heavily advertised (magazine and advertising card) nostrum relied on "testimony" from those who were cured by the "drug," which in fact was 15%–20% alcohol. "Ayer's Sarsaparilla" was likewise a drug to ask your pharmacist for and take if you had dyspepsia and your doctor could not be reached by telephone, as "those tired feelings are frequently the result of an impure, impoverished, or scrofulous condition of the blood …" (Figure 17.3). Some nostrums had alcohol content of over 44%!

In the late 1800s and early 1900s several newspaper, magazine, and book writers earned the title of "muckrakers" for their dedication to searching out and exposing fraud and exploitation ("muck"). One such writer was Samuel Hopkins Adams, who wrote a series of 12 articles for the magazine *Collier's Weekly* under the heading of "The Great American Fraud," beginning in 1905 (http://www.museumofquackery.com/ephemera/oct7-01.htm). The author left no doubt as to the effects of many of the patent medicines, which included drunkenness, death, incapacitation, and so forth, on

FIGURE 17.1 Front side of Pinkham card.



LYDIA E. PINKHAM'S
VEGETABLE COMPOUND
IS A POSITIVE CURE
For all those painful Complaints and Weaknesses so common to our best female population.

It will cure entirely the worst form of Female Complaints, all Ovarian troubles, Inflammation and Ulceration, Falling and Displacements, and the consequent Spinal Weakness, and is particularly adapted to the Change of Life.

It will dissolve and expel tumors from the uterus in an early stage of development. The tendency to cancerous humors there is checked very speedily by its use.

It removes faintness, flatulency, destroys all craving for stimulants, and relieves weakness of the stomach. It cures Bloating, Headaches, Nervous Prostration, General Debility, Sleeplessness, Depression and Indigestion.

That feeling of bearing down, causing pain, weight and backache, is always permanently cured by its use.

It will at all times and under all circumstances act in harmony with the laws that govern the female system.

For the cure of Kidney Complaints of either sex this Compound is unsurpassed.

LYDIA E. PINKHAM'S VEGETABLE COMPOUND is prepared at 233 and 235 Western Avenue, Lynn, Mass. Price $1. Six bottles for $5. Sent by mail in the form of pills, also in the form of lozenges, on receipt of price, $1 per box for either. Mrs. Pinkham freely answers all letters of inquiry. Send for pamphlet. Address as above.

No family should be without *LYDIA E. PINKHAM'S LIVER PILLS*. They cure constipation, billiousness, and torpidity of the liver. 25c. per box. — FOR SALE BY

S. A. SEXTON,
Hopewell, N.J.

FIGURE 17.2 Reverse side of Pinkham card.

users from infants to adults. The use of fake testimonials was exposed as a sales technique. The use of morphine and other opiates and additives (without documentation) was also exposed. The exchange of mailing lists of users was exposed. The use of financial and political pressure to sell advertisements for nostrums was exposed.

The renowned book *The Jungle* was published in 1906. The text amounted to an exposure of the meatpacking industry and the ways workers were treated as well as mistreated. The author, Upton Sinclair, was variously labeled as a result of this and other works as a muckraker and a socialist. This work, however, was based upon his own experiences working in the meat packing industry in Chicago and was based on experiences, in part expressed thusly: "…with the hot weather there descended upon Packingtown a veritable Egyptian plague of flies; there could be no describing this—the houses would be black with them. There was no escaping; you might provide all your doors and windows with screens, but their buzzing outside would be like the swarming of bees, and whenever you opened the door they would rush in as if a storm of wind were driving them." It should be evident to the reader that meatpacking was not a clean affair and, by implication, that spoiled and soiled meat was common. The novel was well laden with such implications.

Public outrage based upon these two authors' publications (and others—too numerous to mention) led to the passage in 1906 of the first Food and Drugs Act under the then president Theodore Roosevelt. It prohibited interstate commerce in misbranded and adulterated foods, drinks, and drugs. The Meat Inspection Act was passed on the same day.

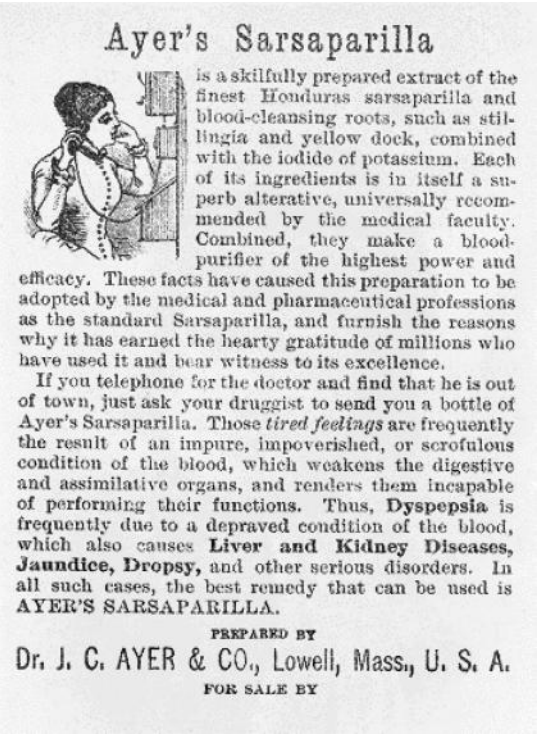


FIGURE 17.3 Reverse side of Ayer's advertising card.

Over the next 30 years, the FDA regulations were slowly added to, with regulations prohibiting false therapeutic claims, requiring labeling of "weight, measure, or numerical count" on foodstuffs and so forth. Limits, in part due to deaths of infants, were placed upon the amount of morphine that could be added to nostrums and other drugs of the day. Record keeping was mandated for physicians and pharmacists who prescribed or filled prescriptions for products containing high levels of narcotics (akin to pseudoephedrine tracking in the early 21st century!). Misleading labeling was condemned. Standards for quality and measure for canned food (excluding meat and milk products) were first promulgated.

The deaths of 105 persons in 1937 were attributed to the use of diethylene glycol to dissolve sulfanilamide (an antibiotic and diuretic compound) in the nostrum "Elixir of Sulfanilamide." Diethylene glycol is chemically similar to ethylene glycol, which is typically used as antifreeze in automobile radiators. Both taste sweet, can dissolve certain other compounds, and can cause death in relatively small quantities. This incident is cited as giving the final impetus to the first comprehensive Food and Drug Act in the United States with its built-in requirement that foods be safe. Specifically, the *Federal Food, Drug, and Cosmetic (FD&C) Act of 1938* as passed by Congress contained the following as new provisions:

1. Extended FDA control to cosmetics and therapeutic devices
2. Required new drugs to be shown safe before marketing—starting a new system of drug regulation
3. Eliminated a requirement to prove intent to defraud in drug misbranding cases
4. Provided that safe tolerances be set for unavoidable poisonous substances
5. Authorized standards of identity, quality, and fill-of-container for foods
6. Authorized factory inspections
7. Added the remedy of court injunctions to the previous penalties of seizures and prosecutions

The period from 1939 to 1962 saw a gradual evolution of FDA powers and responsibilities and related legislation. Food standards were first established, the Public Health Service Act was passed, advertising standards for drugs (regarding false advertising) were tightened, food additives were regulated, hazardous substances labeling was mandated, and many drugs were put on a prescription-only basis. Documentation was additionally required on all factory inspections by the FDA.

Thalidomide is an antinausea and sedative drug that was introduced in 1957 (initially in Germany) to be used as a sleeping pill. It was quickly discovered to help pregnant women with the effects of morning sickness. It was withdrawn from the market in 1962 after being found to be a teratogen, after having caused many different forms of birth defects in thousands of infants. The negative effects of thalidomide led to the development of more structured drug regulations and control over drug use and development. While the FDA did not allow the drug to be sold in the United States, many cases did appear here due to import of the drug. Publicity regarding these births gave support to stronger drug regulations in the United States and abroad, and in the same year, the Drug Efficacy Amendment was passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to the FDA the effectiveness and safety of their products before marketing. Informed consent was required of patients participating in clinical trials, and adverse drug reactions were required to be reported to the FDA. All medicines currently on the market were additionally to be restudied for their safety and efficacy.

Major legislative changes since this time (relative to this text) have largely aimed at improving the ability of the FDA to regulate drug manufacture, drug labeling, and drug distribution and redistribution in order to assure public safety. Of importance to the reader is the current process for drug discovery and testing and the development of combination devices, and the role(s) of biomedical engineering in the design and development of same.

17.2 DRUG DEVELOPMENT

Drug development at the current time is both university driven and industry driven. University programs with such monikers as "Molecular Pharmacology and Chemistry," "Pharmacology," "Chemical and Biomolecular Engineering," "Biotechnology," and so forth study drug development, drug sensitivity and resistance, cell signaling, nanoprobe development, toxicity of materials, and so forth. Most major drug companies run both in-house and university collaborative programs. Most drugs in current use are based upon historical precursors and variations on known chemical libraries that have a bio-effect, as will be mentioned later. Many biotechnology firms deal with working on interactions with not only our own personal genetic makeup but also that of other animal and plants in the development of new drugs, vaccines, and processes.

17.2.1 Native Drug Development and Use

Many drugs that are in the current pharmacopeia are derived from plants that have been used in native medicinal treatments. For example, *Anredera diffusa* (Madeira vine) has been used in traditional Peruvian medicine as a wound-healing agent. A recent analysis of the plant yielded oleanolic acid, which has antitumor and antiviral properties.[1] Curare, likewise, was found in South America as a paralyzing agent used for game hunting. Salicylic acid, a precursor to acetylsalicylic acid (also known as aspirin), is present in a number of fruits and other plants and is best known for its original use as an extract from the bark of the willow tree. Most medicines based upon these discoveries are now manufactured from manufactured compounds, rather than derived from their plant or animal precursor.

17.2.2 Sampling the Environment

Many drugs have been developed based upon studies based upon environmental samples; penicillin, for example, is a fungus that grows on appropriate substrates, such as bread in a damp

environment. First discovered in 1928, it was one of the first useful antibiotics in use in medicine. Environmental sampling programs continue in many parts of the world to try to duplicate this discovery.

17.2.3 Manipulation of Known Reactants

Current opioids ("painkillers") such as morphine have side effects that limit their long-term usefulness. A study of the structure of the molecules involved has led to an analysis of a derivative section named IBNtxA, which, when combined with other transport molecular structures, may be more efficacious in its use (http://www.mskcc.org/blog/findings-could-lead-development-new-painkiller, accessed 2/25/13).

17.2.4 Plants and Animals as Factories for Drug Manufacture

Via genetic manipulation, some plants as well as animals are being used to manufacture drugs. Multiple animal models are being investigated (in lieu of the current egg model), for example, to generate flu vaccines. "Molecular pharming" is being investigated as a tool for drug development in resource-poor environments (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230538/). Biopharmaceuticals have been derived since 1982 from plants (insulin and now over 100 other compounds); genetic modification of the base plants will likely improve yields and types of drugs derived (http://www.ncbi.nlm.nih.gov/pubmed/21412360).

17.2.5 Computer-Aided Development of New Drugs Using Chemical Modeling of Structures

A final frontier at this time in the drug development business is computer-aided drug design. Recent estimates of successful drug discovery to market time and costs of 7–12 years and up to 1.2 billion dollars[2] are causing many companies to develop, in addition to their current efforts, research groups that attempt to model the probable interactions of modeled compounds and known biological constructs and responses. Various universities are offering coursework relevant to this endeavor via departments of bioinformatics, pharmacology, biochemistry, and the like. In principle, this approach should lead to shorter "discovery to test" phases and should improve on the reliability of discovery as approaches are refined.

17.2.6 Other Approaches: Nanoparticle and Microparticle Hybrids with Drugs

Some recent activity related to drug development and delivery under study involves nanoparticle and microparticle hybrids with drugs. The reader is referred to survey articles on this topic as undergraduate design projects are not likely to involve this technology.[3]

17.2.7 The Role of Imaging in Preclinical and Clinical Drug Development

Imaging technologies are also useful tools in the development of new drugs and related technologies. The basic premise is that imaging tools (and test subjects) can be developed such that, for the development of a new therapeutic, that "proof of target" (did the drug go where it is needed?), "proof of mechanism" (did it do what it was designed to do?), and/or "proof of efficacy" (did it do what it was designed to do?) can be shown.[4] The imaging tool development stage might include the replacement of normal carbon in the test compound with carbon-11 (a positron emitter) or with fluorine-18 (also a positron emitter), injection of the material into the test animal, and imaging of the uptake and distribution of the isotope (and, by inference, the drug being tested) and analysis of the metabolites resulting from the test.[5] Proper selection of the test subjects (for example, mice) and early testing

can greatly affect the "bottom line" of a new drug development effort by allowing better and earlier "stage-gate" (go/no-go) decisions to be made.

17.3 DRUG TESTING

Once a drug candidate is identified, a series of steps must be undertaken prior to testing on humans and later marketing. Most of what will be discussed here is mandated by FDA considerations as outlined here. The pathway details will depend on the type of material developed (drug or vaccine, for example) and the availability of suitable animal models for the treatment or disease studied.

17.3.1 Initial Screenings

Initial screenings of a material (if necessary, for example, for a "found material") can be very straightforward using test-tube or petri dish preparations. Does the material inhibit penicillin growth? Does it show antibiotic effects? Does it inhibit cellular division? Is there anything about the material that is unexpected?

17.3.2 Primary Animal Studies

Most of the time, the major part of the drug study will involve testing of the drug material in *at least* one rodent *and* one nonrodent relevant animal model. Most of the time, the rodent model is the mouse.

Mice, generally, are used as they generally show similar responses to most medicines as humans do. Additionally, they have very brief gestation times (19–21 days) so that any material that might show teratogenicity might be caught fairly early in studies (such as with thalidomide). If warranted, specially bred mice can be purchased that have had genetic modifications to target organs to more closely mimic certain human conditions; otherwise, mice are an inexpensive testing platform. The use of rats is generally second only to mice.

The second (and higher) choice of animal might include one of the following: chimpanzees, cats, dogs, rats, primates, rabbits, pigs, sheep, ferrets, woodchucks, armadillos, guinea pigs, lobsters, chinchillas, electric eels, opossums, angler fish, axolotl, slugs, pigeons, shark, zebra fish, tropical fish, trout, goldfish, *Caenorhabditis elegan*s, fruit flies, worms, frogs, horseshoe crabs, and so forth. Each has some special "niche" where their response is similar to a human's and is thus potentially of value to human medicine. (The armadillo, for example, can contract and pass on leprosy.) The cost factor varies considerably and can greatly affect the drug study's overall business plan.

Additional costs are involved in maintaining animals covered in the U.S. Animal Welfare Act. Many animals fall under this act and thus must be maintained in housing that meets certain standards and may only be worked with under the guidance of an animal care committee, and so forth. Rats and mice and "cold-blooded" animals are excluded. When animal testing is done to support applications for medical products regulated by the FDA, manufacturers or sponsors are required to follow the FDA's regulation, Good Laboratory Practice for Nonclinical Laboratory Studies (21 *Code of Federal Regulations* [CFR] part 58). The FDA also supports the use of independent animal care and use committees (IACUC) for laboratory studies involving animals.

The first, second, and higher choice of animal targets for drug research must be justified for the drug and treatment(s) attempted; all data collected will be subject to review by the FDA should human studies be requested.

For drugs and biologics, the focus of animal testing is on the drug's nature, chemistry, and effects (pharmacology) and on its potential damage to the body (toxicology). Animal testing is used to measure

- How much of a drug or biologic is taken up by the animal by whatever means it is administered (oral, skin absorption, injection, etc.)
- How a medical product is broken down chemically in the body (metabolism, by-products)

- The toxicity of the product and its breakdown components (metabolites), including such data as LD50 (lethal dose for 50% of animals dosed) and teratogenicity (potential for birth defects)
- How quickly the product and its metabolites are excreted from the body (kinetics)
- If the animal is an appropriate model, whether the biologic has any useful side effects

17.3.3 Investigational New Drug Application and Human Subject Solicitation

If the biologic material has the desired effects on the studied animal models, the developer may then petition the FDA for testing of this new drug. All data and supporting material must be submitted to the FDA for review; documentation of the proposed testing methods (protocols and consent documents) must further be part of the Investigational New Drug (IND) application. Studies must be done under the supervision of a human subjects committee; screened subjects must supply consent via a signed consent form.

Screened subjects are those volunteers who meet eligibility criteria for entry into the study. Generally, this includes the "class" of patients most likely to benefit from a useful outcome of the study, but not necessarily. A partial listing (partially redacted verbatim) seen by this author for a particular study follows:

… eligibility criteria to be sure you will qualify for the study:

- Must be male or post-menopausal female between 65 and 85 years of age.
- Cannot have been hospitalized or had a worsening of a disease in the last 12 weeks.
- Cannot have donated blood or plasma in the last 12 weeks.
- Cannot have any history of inflammatory bowel disease or autoimmune disease.
- Cannot have any history of chemotherapy, immune system–suppressing drugs, long-term systemic steroid use (greater than 7 days), or disease-modifying antirheumatic drugs (DMARDS).
- Cannot currently have cancer, COPD, oxygen use, kidney failure/dialysis, unstable heart disease, HIV, hepatitis B or C.
- Chronic medical conditions must be stable for at least 12 weeks.
- No previous receipt of *XXXXXXXXX* vaccine.
- No proven or suspected *XXXXXXXXXX* infection in the last 6 months.
- No receipt of blood products or immunoglobulins in the last 12 months.
- Cannot be on anticoagulant, antiplatelet or antithrombotic therapy (heparin, warfarin, sore) (aspirin is allowed).

- …

The consent form will supply (typically, and at a minimum) most of the following information: principal investigator's name, study title, institution name, dates of IRB approvals and expirations, and the following labeled sections (and their embellishments).

1. What is the purpose of this study?
2. What will happen and how long will you be in the study
3. Costs to you if you take part in this study
4. Side effects and risks that you can expect if you take part in this study
5. Risks that are not known
6. Payments in case you are injured because of this research study
7. Good effects that might result from this study
8. Other treatments you could get if you decide not to be in this study
9. Payments for your time spent taking part in this study or expenses

10. Reasons the doctor may take you out of this study
11. What will happen if you decide to stop being in this study?
12. Who to call for any questions or in case you are injured
13. Clinical trials registry
14. Confidentiality
15. Authorization to use/disclose protected health information

This information is typically followed by areas for the volunteer's and witnesses' signatures and date.

17.3.4 Drug Testing in Humans, Phases I, II, and III

Assuming the aforementioned studies auger well with the developer, the FDA may grants a new drug investigation permit for use on humans. Drug testing normally follows three phases as outlined here, with the proviso that all untoward events are reported and, if the effects are bad enough, the study must be stopped.

17.3.4.1 Phase I

A small group (20–100) of *healthy* volunteers is given the drug to see

- If it is safe
- How quickly it is absorbed, metabolized, and excreted from the body

This cohort, in practice, allows one to test if scaling of doses (from mouse to human, for example) was correctly done, tests for the chance that reactions may occur in a large fraction of the population, tests that uptake and excretion estimates are correct, and (obviously) allows for the first reporting of any previously unknown side effects (as was found for Viagra). The primary concern here is *safety.*

17.3.4.2 Phase II

A group (100–300) of volunteer *patients* with the disease (or condition) are given the drug to see

- How effective it is against the signs and symptoms of the disease (*efficacy*)
- What doses are best (*dosage*)
- What side effects may occur (side effects, reactions, future warnings, risks…)

A *control group* of similar size may be given a dummy drug (placebo). Ideally, the trials are "blinded," with neither the subjects nor the investigator knowing which pill a subject is receiving. This technique can augment the statistical significance of claims made regarding the drug's efficacy. The low numbers (still) at this point do not yet guarantee that a drug is safe for a reasonable percentage of the population. If the phase II trials indicate that the drug may be effective—and the risks are considered acceptable, given the observed efficacy and the severity of the disease—the drug moves to phase III.

17.3.4.3 Phase III

In these trials, 1000–3000 *patients* with the disease are given the drug to get more reliable data on its

- Effectiveness
- Safety
- Dose response
- Other side effects (and potential uses)

If appropriate, these data must be compared with the drug(s) that are currently used for the disease. Once these studies are completed, there will be an initial review of the drug safety and efficacy data collected by the sponsor with the FDA. A new drug application is filed, a formal review of the application is scheduled, the labeling for the new drug is reviewed, and the facility for the drug manufacture is inspected. Once all steps are properly completed, the drug can be approved for sale.

As mentioned, the time from discovery to market is 5–7 years. Patent protection (if any) is 20 years from the date of filing; thus, drug manufacturers have a severely limited time to recoup their investments in drug development. A ploy to extend the patent by making minor changes in the compound (or compounding) has been used in some cases to extend the payback time. A 2013 case in India may severely limit this tactic.

17.4 FDA POSTPRODUCTION OVERSIGHT AND ENFORCEMENT

Even after a drug is available for prescription, its use should be carefully monitored and unexpected side effects reported (e.g., thalidomide and Vioxx). Continuing oversight of an approved drug is called postmarket surveillance or phase IV trials. If untoward events are seen (birth defects in the case of thalidomide, increased risk of heart attack with Vioxx), the FDA has the power to stop distribution of the drug, force recall of same, and/or fine the manufacturer.

Sometimes, formal phase IV trials are conducted after a product is already approved and on the market to find out more about the treatment's long-term risks, benefits, and optimal use, or to test the product in different populations of people, such as children.

17.5 THE FUTURE OF DRUG THERAPY?

It has been postulated that one of the future trends in drug therapy will be individualized therapies based upon an individual's genome, often referred to as personalized medicine. With the cost of genome sequencing approaching $1000 or less (post 2013), the benefit of paying for a complete sequence might soon far outweigh the risk taken by patients and physicians currently with broad-spectrum antibiotics and the like. Likewise, the ability to predict both personal risks for diseases and the risk(s) of passing on genetic profiles to offspring may determine future marriage and reproduction choices.[6]

The use of "nanoliter bioreactors" containing specific human cell lines (such as heart, kidney, lung, nervous system) may prove to be of value in the future testing of drugs and drug derivatives, as well as in the testing of environments for safety (akin to the use of canaries in coal mines). As a side effect of this work, if it is successful, the use of multiple animal models for testing of new drugs may be modified, with a potential effect of placation of People for the Ethical Treatment of Animals (PETA).

17.6 THE FDA AND COMBINATION PRODUCTS

A relatively new purview of the FDA is the regulation of combination products. A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, a device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include the following:

1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity (e.g., drug-eluting stents, coated metal implants)
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (surgical trays, drug plus delivery device)

3. A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose) (laser and sensitizing compound)
4. Any investigational drug, device, or biological product packaged separately that, according to its proposed labeling, is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

The Office of Combination Products in the FDA has the responsibility to develop guidelines for the review of combination products and to assign such devices to the (assumed) appropriate primary review unit (drug or device) in the FDA. As necessary, this office coordinates dual reviews.

17.7 VETERINARY MEDICINE

The FD&C Act gives the FDA the legal authority to approve and regulate drugs for animals. Before a drug company can market an animal drug, the company must get the drug approved by the FDA. To get FDA approval, the drug company must prove that

- The drug is safe and effective for a specific use in a specific animal species. If the drug is for use in food-producing animals, the drug company must also prove that food products made from treated animals are safe for people to eat.
- The manufacturing process is adequate to preserve the drug's identity, strength, quality, and purity. The drug company must show that the drug can be consistently produced from batch to batch.
- The labeling is appropriate and truthful. The drug company must make sure that the labeling contains all necessary information to use the drug safely and effectively, including the risks associated with the drug.

The FDA's role does not stop after an animal drug is approved. As long as the animal drug is marketed in the United States, the FDA continues to monitor the following:

- The drug's safety and effectiveness
- The drug's manufacturing process, to make sure quality and consistency are maintained from batch to batch
- How the drug is marketed, to make sure the advertisements are truthful and not misleading

17.8 THE FDA AND COSMETICS

The FDA also has authority over cosmetics. The two most important laws pertaining to cosmetics marketed in the United States are the FD&C Act and the Fair Packaging and Labeling Act (FPLA). The FD&C Act prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce. Violations of the act involving product composition—whether they result from ingredients, contaminants, processing, packaging, or shipping and handling—cause cosmetics to be adulterated and subject to regulatory action. Under the FD&C Act, a cosmetic is adulterated if

- "It bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under conditions of use as are customary and usual" (with an exception made for hair dyes)
- "It consists in whole or in part of any filthy, putrid, or decomposed substance"
- "It has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health"
- "Its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health"
- "It is, or it bears or contains, a color additive which is unsafe within the meaning of section 721(a)" of the FD&C Act (except for hair dyes) (FD&C Act, sec. 601)

Improperly labeled or deceptively packaged products are considered misbranded and subject to regulatory action. Under the FD&C Act, a cosmetic is considered misbranded if any of the following are true

- Its labeling is false or misleading in any particular
- Its label does not include all required information
- The required information is not adequately prominent and conspicuous
- Its container is so made, formed, or filled as to be misleading
- It is a color additive, other than a hair dye, that does not conform to applicable regulations issued under Section 721 of the FD&C Act
- Its packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970 (FD&C Act, sec. 602)

In addition, under the authority of the FPLA, the FDA requires an ingredient declaration to enable consumers to make informed purchasing decisions. Cosmetics that fail to comply with the FPLA are considered misbranded under the FD&C Act. The FDA's legal authority over cosmetics is different from other products regulated by the agency, such as drugs, biologics, and medical devices. Cosmetic products and ingredients are not subject to FDA premarket approval authority, with the exception of color additives. However, the FDA may pursue enforcement action against violative products or against firms or individuals who violate the law.

Cosmetic firms are responsible for substantiating the safety of their products and ingredients before marketing. Failure to adequately substantiate the safety of a cosmetic product or its ingredients prior to marketing causes the product to be misbranded unless the following warning statement appears conspicuously on the principal display panel of the product's label:

> Warning—The safety of this product has not been determined (21 CFR 740.10).

In general, except for color additives and those ingredients that are prohibited or restricted from use in cosmetics by regulation, a manufacturer may use any ingredient in the formulation of a cosmetic provided that the ingredient and the finished cosmetic are safe, the product is properly labeled, and the use of the ingredient does not otherwise cause the cosmetic to be adulterated or misbranded under the laws that the FDA enforces.

The FDA may take regulatory action if it has information to support that a cosmetic is adulterated or misbranded. The agency can pursue action through the Department of Justice in the federal court system to remove adulterated and misbranded cosmetics from the market. To prevent further shipment of an adulterated or misbranded product, the agency may request a federal district court to issue a restraining order against the manufacturer or distributor of the violative cosmetic. Violative cosmetics may be subject to seizure. The FDA also may initiate criminal action against a person violating the law.

The FDA is also active in responding to false claims made for products. For example, in 2012, the seller of a "night cream" made claims that the use of the cream would "boost the activity of your genes" and "stimulate cell production to reconstruct skin to a denser quality." Additional testing was claimed on "over 4000 genes." These claims, under FDA definitions, were those applicable only to drugs and, as such, meant that the cream could not be sold without clearance as a drug. Failure to document a changing of this advertising within 15 days of the FDA notification put the advertiser at risk for injunctions and seizure of all product (http://blog.aarp.org/2012/09/12/anti-aging-skin-creams-fda-warns-about-label-claims/print, accessed 9/19/2012).

17.9 SUMMARY AND CONCLUSIONS

The purpose of this chapter has been to acquaint the reader with the primary nondevice history and regulations involving the FDA as might impact the reader of this text. It is highly likely that your career—even if your current design project does not involve material in this chapter—and/or private life will be affected by the material herein. Nostrums, false advertising, drug errors, and extensions of the truth seem to be a part of life in this society. Witness, for example, the information on the sign in Figure 17.4.

As listed, under the heading of "Stress FREE with natural herbs and reflexology," the 10 benefits of foot massage are as follows:

1. Strengthen body
2. Beneficial against neurocism and insomnia
3. Beneficial against hypertension
4. Prevent numbness of legs
5. Prevent rheumatoid arthritis
6. Beneficial against diabetes
7. Prevent common cold
8. Promote weight loss
9. Prevent cerebral vascular clot
10. Relax the body and mind

FIGURE 17.4 Foot spa advertisement—Nashville, TN.

A brochure from the same company claims "10 benefits of reflexology":

1. Relieve arthritis pain
2. Alleviate migraine, headache, and chronic sinusitis
3. Promote weight loss
4. Reduce premenstrual pain for women
5. Improve sleep quality
6. Lower high blood pressure
7. Beneficial against diabetes
8. Eliminate digestive disorder
9. Prevent cerebral vascular clot
10. Relax the body and mind

Needless to say, some of these claims border on drug claims and are not appropriate under FDA rules.

EXERCISES

1. Fluorescent proteins have been inserted into various life forms in order to study various functions. Find and report on one of these and discuss the potential ramifications of the work.
2. Find and discuss an example of the use of epigenetics in drug development.
3. Find and report on the use of bioreactors in the detection of pathogens.
4. Find and report on the use of bioreactors in the development of drug testing.
5. Ayer's Sarsaparilla and Lydia Pinkham's Vegetable Compound were both made in Massachusetts. Contrast these drugs with the recent debacle (2012–2013) involving the company "New England Compounding."
6. Research and briefly report on any recent drug recall.
7. Research and report on any recent fine involving a drug company.
8. Lipitor went off patent protection circa 2011. One of the first companies to make a generic form of this drug was Ranbaxy of India. What problems did Ranbaxy have with this drug, and what was the FDA's involvement?

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18 Biological Engineering Designs

> It is arrogant, reckless, and hazardous to make value judgments on the significance of a species.
>
> **Charles F. Lovell Jr.**

Engineering designs involving living things are interesting and challenging, perhaps so because the behavior of biological entities can only be partially anticipated. For the most part, designing using or applied to biological systems uses many of the same approaches and procedures necessary for biomedical designs meant mainly for human health care. The biggest difference, however, is in the range of possible objects of the design, just as the extra challenges of veterinary medicine compare to those related to human medicine. So, the information presented in this chapter is meant to supplement, not supplant, the materials presented elsewhere in this text. This chapter is meant to broaden horizons for the reader beyond those for a single species.

18.1 WHAT IS A BIOLOGICAL SYSTEM?

The definition of biological engineering by the Institute for Biological Engineering (IBE) is as follows:

> Biological engineering is the biology-based engineering discipline that integrates life sciences with engineering in the advancement and application of fundamental concepts of biological systems from molecular to ecosystem levels.

Biology includes all living things, and biological engineers may propose designs using any of them or for any of them. The area of biological systems ranges from the very smallest organisms to the largest ecosystem. It also includes substances made from or derived from living organisms, such as biochemicals, foods, or biofuels. Living things may be the object of the design, a means to implement the design, or a by-product of the design. This broad range of possible subjects poses special challenges for biological engineers attempting to formulate a design, because there is often less known about the biological subject than there is about human beings. Many biomedical engineering designs have evolved well beyond the first prototypes into a highly empirical stage. The lack of much empirical knowledge about specific biological subjects means that many biological engineering designs must depend more on generalizations and basic principles than do biomedical designs meant for human patients. For this reason, it is especially important for biological engineers to be familiar with general biological principles.

Biological engineers can deal with biological systems as diverse as plants, animals, microbes, proteins, and so forth. Putting all these together to form unique biosystems means that biological engineering designs involving those biosystems must be able to anticipate the contributions of each entity to those biosystems in order to achieve the design objectives. It is certainly easier to deal with just one species than many species together, and sometimes, that is possible, but often, the design cannot avoid interspecific interactions.

18.2 SPECIAL ISSUES WHEN DEALING WITH NONHUMAN SUBJECTS

18.2.1 Difficult or No Direct Communication

The biological engineering design could be involved with plants, microbes, lower animals, or even food substances. In none of these cases is it possible to communicate directly with the object of the design. There are biomarkers that are being discovered to suggest the conditions of the noncommunicative living objects, but these are but indirect indicators of the states of environmental stresses on the biological entities. As approximate as these biomarkers are, they still allow the designer to be aware of at least some aspects of the state of the living things of concern. There are biomarkers for stress levels in aquatic species, plants, microbes, and foods. Biomarkers are also being developed as indicators of certain diseases in many species, including humans.

Of course, communications with humans can also be a problem at times. Unconscious patients are unable to give verbal or written replies to questions, as are patients who are conscious but otherwise unable to speak. Some biomedical devices are designed remotely from the eventual users, so direct responses are also not possible. But many of the best designs require feedback from the patient in order to adjust the design for optimal performance. Some communication is often necessary.

The same is true for nonhuman species. A design for microbial bioremediation to clean up environmental pollutants, for instance, is often produced open loop, without feedback. Environmental conditions thought to be necessary for the growth and activity of particularly useful naturally occurring or introduced microbes are provided with the understanding that these conditions normally result in the desired outcome. Environmental monitoring for pollutant concentration must be performed on a regular basis to assure that the bioremediation proceeds as designed. This provides the necessary feedback and allows adjustments to be made if necessary. Direct communication with the microbes is not possible, but other means can be found to provide the necessary assurance that the design is achieving its goals.

18.2.2 Awareness Issues

Sentient creatures are those who are aware of themselves and their surroundings in a conscious way. Normal humans are sentient beings. There have been questions and studies related to sentience in other species, and recent results seem to indicate that more advanced animals may also have sentient qualities. One test that has been used is the mirror test, where a mark is placed on the face of an animal and the animal is shown its reflection in a mirror. If the animal recognizes that the mirror image is of itself, and a strange mark appears on its face, then the animal has at least some degree of sentience.

All living organisms, from the simplest prokaryotic cell to the largest multicellular plant or animal, sense their environment. There are ligands on the cell surface to detect the presence of important chemicals in the cell surroundings; there are also optical sensors possessed by the simplest of plants or animals. One defining feature of living things is the ability to sense their environments, react to them, and, perhaps, to anticipate environmental influences. Sentient animals go beyond that by having some sense of past, present, and future tenses, and being able to connect emotionally with other beings either present or absent.

The ability to design a successful system is much simpler if the living beings involved in the design are not sentient. Sentient beings are afforded higher moral status by humans than are nonsentient beings. This is not the same as saying that the nonsentient being is insensitive, because we know that all living creatures have sensitivity to environmental stimuli. Thus, a robotic surgery machine intended for a flatworm could be simpler than one intended for a dog.

The degree of awareness of pain and stress for different biological organisms varies as much as the systems do themselves. The biological engineer must be aware of these differences when dealing with different types of living creatures.

18.2.3 Presumption of Status

As egocentric humans, we attribute various levels of status to those other creatures with which we come in contact. Most humans generally have the highest regard for other humans, somewhat less regard for our mammalian pets, less esteem for lower animals, some regard for plants, and almost no regard for microbes. Of course, there are individual exceptions to this generalization.

More care must be taken in biological engineering designs that involve those creatures normally considered to have higher status. Biological engineers must be more careful to assure that higher-level creatures do not suffer undue pain, are euthanized humanely, and are not subjected to high levels of avoidable stress. On the other hand, there is no such care given to individual microbes in a bioreactor, where the microbes are often harvested and destroyed to release useful biochemicals.

There are exceptions to this presumption of status by certain special interest groups of humans, and the biological engineer must be aware of the impacts of her or his design viewed through the eyes of these groups. Groups such as the People for the Ethical Treatment of Animals (PETA), the Humane Society of the United States (HSUS), the Sierra Club, and others may consider certain rights to be attributed to certain species and thus make certain design options unattainable. Designs that affect whole ecosystems can be criticized by groups unwilling to expose a threatened species to extirpation (e.g., the snail darter or northwestern spotted owl). Designs for livestock handling systems can be opposed by HSUS, while designs involving animal research may be assailed by PETA. There may even be some groups with special interest in the welfare of certain plants. These groups can greatly influence the types of designs considered feasible.

18.3 UNINTENDED CONSEQUENCES

Living systems are not passive: they move, they change, and they influence their surroundings. Thus, they cannot be used blindly without expecting other changes to happen. Anticipating these other changes can distinguish those who are experts in biological engineering from others possessing casual knowledge. Whether the process involves installing an artificial heart into a sick human patient or introducing a new law to limit harvesting of a wild food species, there will be other unrelated and perhaps unseen consequences.

The biggest problem with unintended consequences is that not only do they cause the design to be unsuccessful, but also, their ill effects may go far beyond the confines of the design, especially if the design makes the larger ambient environment accessible. Introduction of alien species, such as rabbits in Australia, African honeybees in Brazil, gypsy moths in New England, or kudzu in the southeastern United States, can be disastrous. That is one reason why the introduction of genetically modified microbes into the environment is being so closely watched and regulated. Damming a river, draining a swamp, or clear-cutting a forest can also have severe consequences. Even applying a new medical device to a patient who has acclimated to a poorly functioning organ will have some unwanted effects. All of these possibilities need to be thought about before the design is finalized.

18.4 ENVIRONMENTAL INTERACTIONS

Biological systems do not exist in isolation. There are relations with a physical environment, with a chemical environment, and with other living things. These other biological units (BUs) may be at the same hierarchical level as the target BU, as between a vegetable plant and a weed in a garden, or as between two hepatic cells in the liver. They may also be at different hierarchical levels, as with an ape in a forest ecosystem.

No matter what the arrangement, the interactions are many. Each BU (defined as a biological system at some hierarchical level) affects and is affected by both its biological environment and its physicochemical environment (Figure 18.1). The presence of other BUs in the same physicochemical environment changes the physicochemical environment for the target BU, so that environmental

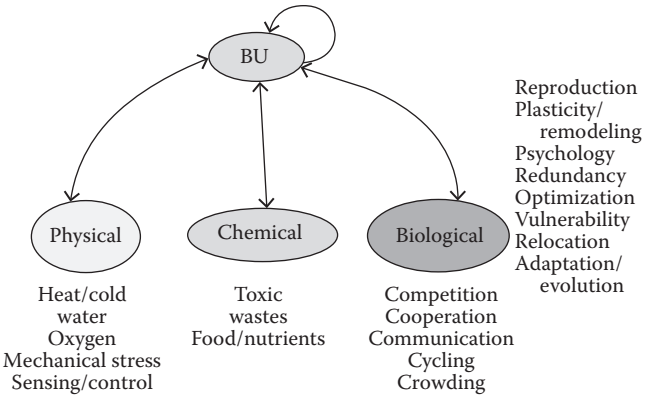

FIGURE 18.1 Many interactions with the environment are possible. The presence of other biological units (BUs) can affect a target BU directly or indirectly through their environmental responses. Listed are some of the typical environmental interactions encountered by a BU.

conditions are constantly changing. Equilibrium is never reached, and a true steady state, where changes over time are nil, is rare and not long-lasting when it does occur. Thus, being able to predict typical responses is about all that can be expected.

Biological responses are very much determined by the context in which they occur. Each BU is not isolated, and a BU that adapts one way to one type of environment can adapt another way to a different environment as long as the environment can be sensed in some way; thus, sensing and communications are very important.

It is easy to understand that BUs are affected by the environment but harder to realize that BUs may have a profound effect on the external environment in which they are located. But plants often emit substances into the soil surrounding their roots in order to make necessary nutrients more available, synergistic combinations of organisms give all participants survival advantages, large African herbivores have turned forests into savannahs, and microbial metabolism produces water as a by-product in a place that promotes further microbial growth. No environment that contains living things is the same as it would be with no life. When incorporating living things into a design, the environment in which the designed system is placed will affect the design, but the environment will also be changed.

18.5 BIOLOGICAL PRINCIPLES

Biological engineering designs may be successful when the designer has little or no knowledge of biology, but the chances of this happening are exceedingly small. Knowing what to expect from a biological system that is part of the design is one means to mitigate the unintended consequences that often arise when living organisms are placed in any controlled environment. Even if the biological system of interest is well known, and the design is relatively simple, knowing what to expect from the system, and what things could possibly go wrong with the system, can go a long way toward a successful design. After all, the means to a successful engineering design are through the ability to predict outcomes of something that has yet to exist.

Just as there are many possible forms of a biological engineering design, so are there different biological principles relevant to the design. Principles relevant to microbes in a highly controlled bioreactor environment are somewhat different from those related to bioremediation microbes in an outdoor environment. Principles used for a design of a housing facility for dogs and cats differ somewhat from principles for housing of rare spiders. Principles for designs for nonliving liquid foods can differ from those for living fluids such as blood. Principles for an aquatic species may be somewhat different from those for a dry land species. There is often some specialization that takes

place among biological engineers who acquire useful knowledge about working with particular species, in particular environments, and with particular applications. However, there are some general principles of biology that apply to most, if not all, possible applications. These will be given in the following sections.

18.5.1 The Basic Principle: Survival and Reproduction

The first principle of biology is the imperative for survival and reproduction. There is absolutely nothing as important to a living organism as this. Life is precious for living creatures, and they will do almost anything, make any modifications (remodeling), and react in multiple ways to remain alive. There is a limit, however, to the adjustments that can be made, and going beyond that limit results in death. Although it is very difficult to define exactly the dividing line between living and nonliving, the result of something clearly seen as living when it becomes nonliving is that it can no longer survive and reproduce. This applies not only to individual organisms but also to complexes of organisms such as synergies, ecosystems, and tissues.

18.5.2 Flexibility

Living creatures can adjust to their physical, chemical, and biological environments, at least within certain limits. Living things are complex combinations of simple mechanisms, all highly tuned to support and complement each other. When a standard mechanism, usually the most efficient one, is no longer able to deal effectively with the present environmental situation, then supplemental mechanisms, usually more costly to the organism, can take over the necessary function. Thus, when stress on a living cell becomes too great, and the basic DNA or proteins that the cell relies upon for its normal activities are in danger of structural damage (denaturation), then heat stress proteins are produced to limit and repair some of the damage.

This flexibility comes at a cost to the creature but allows the creature to survive environmental onslaughts. The first principle given prior can be maintained. This flexibility is also the foundation for bioreactor designs using cells to produce biochemicals useful for human activities, perhaps for medical, safety, or industrial purposes. Cells in bioreactors are often induced by environmental manipulation to produce biochemicals that they would ordinarily not produce in useful quantities. This is part of metabolic engineering.

18.5.3 Redundancy

Enabling the flexibility discussed previously are redundant mechanisms and structures in living things. There are redundant sensors, biochemical pathways, muscles, and organs. The principle of redundancy is important for the reliability of all engineering designs, not just those involving living things. Space vehicles rely on redundant modules in order to remain operational when it is inconvenient or impossible to repair a primary mechanism. The same would be true for designs intended for remote locations on Earth. Biological creatures demonstrate redundancy to a high degree in order to support the first principle given prior. Failure rates of modern industrially fabricated devices, such as automobiles and computers, can be shown to follow the same characteristic curves as human death rates because all have a certain degree of redundant but faulty parts.

18.5.4 Competition

Most living things exist in a highly competitive environment. If the physical and chemical environments are benign enough to sustain life, then there are usually one or more species that can live there. There is almost no time when an environment comprises unlimited resources necessary for growth and reproduction. Thus, every creature living there must compete against others to capture

as much of the limited resource as possible. Even if there is only one species involved, members of that species compete against each other.

The principle of competition can sometimes be used to advantage by biological engineers. When one group of microbes competes successfully with another, the result is called "competitive inhibition." Competitive inhibition is what keeps the dangerous microbe *Staphylococcus aureus*, commonly living on human skin, from overwhelming the human immune system and causing deadly staph infections. Competitive inhibition has also been used to produce sprays to protect fruits and vegetables against microbial populations that cause plant diseases. Competitive inhibition is a powerful natural technique that can be used in many other instances to solve biological and medical problems.

The opposite of competition is cooperation, and this has been found to be important for health and safety reasons. Microbes can form communities called biofilms in which, together, they contribute in different ways to local environments more conducive to their well-being than the surrounding environment in general. These microbes of different species each produce part of the environment, some producing protective coverings, others producing chemicals to neutralize environmental toxins. Biofilms are important for food safety because they can contaminate human food but are extremely difficult to eradicate. The tartar on human teeth is also a biofilm that can cause dental decay.

Other forms of cooperation exist among species as well and are important for some biological engineering designs. Synergistic cooperation can give a combination of organisms the ability to survive and thrive in cases where neither could survive well by itself.

18.5.5 Optimization

The severe competitive environment in which most creatures find themselves leads to a premium placed on comparative advantage. Living things use energy very intensely in order to maintain the internal environmental order characteristic of life, but energy is usually one of the most limited of external resources (along with space and nutrients). Hence, saving a small amount of energy in ordinary activities can give a large competitive advantage and a large payoff for survival and reproduction.

Many biological activities are optimized to take the most advantage of limited resources. This ranges from genetic variability to energy expenditure during breathing to sharing of nutrients in an ecosystem. The amount of the resource saved does not have to be much, just more than that of the competitors.

There is an apparent conflict between optimization and flexibility and redundancy. Biological optimization can be narrow or broad; if the optimum condition is very narrow, meaning that the cost is high of a state not quite at the optimum, then flexibility of the condition is low; if the optimum is broad, then the cost is not great for small deviations from the true optimum point. Biological optima are mostly broad.

Synthetic biology can be used to optimize certain living things to produce desirable products. Algae or other organisms can be optimized, for instance, to produce commercial quantities of biofuels. Synthetic biology has been used to delete unnecessary genes from these organisms to make them more efficient at producing the bioproducts of interest. In this case, the genetic flexibility of these organisms has been reduced to the bare minimum, and, as long as the environment in which they grow can be closely controlled, they do not need the capacity to be flexible or to compete against other organisms.

18.5.6 Communication

Living creatures are constantly sensing the environment and reacting to environmental challenges. Many biological sensors react not only to the level of its stimulus but also to the rate of change of the

stimulus. This gives some ability to sense the direction and severity of changes before they happen, with survival advantages for the organism.

Communication is sensation that invites response. So, in the sense that simple creatures can react to their environments, this is communication at an elemental level. The microbes in a biofilm communicate among themselves to the benefit of each. Other bacteria, such as *Vibrio cholerae*, which causes cholera, communicate by quorum sensing wherein small amounts of chemical markers are emitted by each and the bacterial community takes coordinated actions based upon the concentration of these chemical markers. The organs of the body of an animal communicate remotely through circulating hormones. Communication between the sexes is especially important for courtship rituals. Plants communicate through volatile chemical releases to synchronize breeding (called "masting" in trees) and warn against attacks of insects (often releasing salicylic acid into the air).

Communication among individuals of the same species, especially from mother to offspring, is important to pass cultural information from one generation to the next. Learning is very important for the well-being of more advanced animals; the young learn which things are good to eat, what plants and animals to avoid, and the locations of water, salt, and other minerals. Predator animals learn how to circumvent protective measures taken by prey animals, and animals that learn to escape confinement can teach others how to do it, too. Male birds learn from their elders the proper way to sing their songs to attract female attention but not upset rival males.

More intelligent animals require mental stimulation to avoid boredom. Bored animals sometimes fight and hurt each other. Good biological engineering designs for confinement of intelligent animals should incorporate means to occupy the animals to avoid problems.

18.6 CHARACTERISTICS OF BIOMATERIALS

Sometimes, biological engineers are required to deal with materials of biological origin. Dealing with these is different from imposing unnatural materials on or in the body; in that case, the material is subject to the same constraints as in biomedical engineering design given in a previous chapter.

There are some generalizations that can be made about materials of biological origin. First, solid materials are usually not strictly Hookian; that is, material stress is not proportionate to material strain. Many solid biomaterials have a stress–strain (or pressure–volume) curve that is *S*-shaped. The material is most compliant in the center of the curve; it becomes noticeably stiffer at each end. This characteristic is to be expected unless information is available to the contrary.

Biomaterials differ in surface energy. This is the ability of a material to stick to other materials. High-surface-energy materials stick readily. Mussels exude material with good sticking ability so that they may adhere to underwater surfaces. Low-surface-energy materials do not stick but slide easily with low friction. Some cartilage materials are like that.

Fluid biomaterials are usually non-Newtonian; that is, they do not exhibit constant shear stress to rate of shear relationships. Many biofluids of suspended long-chain protein and polysaccharide molecules are pseudoplastic. That means that they are easier to move the faster they go. Whole blood is a pseudoplastic. Some biofluids with suspended grainy particles act as dilatant fluids. That means that they are easiest to move, have the smallest amount of friction, when moved slowly. Some honeys are dilatant. Some biofluids are rather solid until they are forced to move after some yield stress is reached; these are called Bingham plastics. Other biofluids can change their shear stress rate of shear characteristics over time, such as thixotropic and rheopectic fluids. There are also viscoelastic fluids that spring back with time.

No matter what the material, if it is derived from a living organism, then it will have some complexity to be accounted for in the design.

18.7 DESIGN OBJECTIVES

18.7.1 Effectiveness

Above all, biological engineering designs must be effective. The design goals must be attained. Sometimes, this requires additional care and expense. There are many constraints on a design involving living things. These designs are not always more constrained than designs involving human patients, but the constraints may be different depending on whether or not special interest groups could be involved.

18.7.2 Economics

Successful engineering designs are as economical as possible. Designs that can achieve the same set of goals, but less expensively, survive in the economic marketplace. Many biological engineering designs are unique, and economics becomes secondary to effectiveness, but some biological engineering designs are meant to be mass-produced. In that case, economics is important.

18.7.3 Sustainability

Sustainability, as a design objective, means minimal environmental impact and the use of renewable resources. A biological engineering design is sustainable if the designed process could be operated continuously and indefinitely without running out of input resources, including energy. Because the second law of thermodynamics precludes strict sustainability, some renewable resources will be necessary for a sustainable design. Thus, energy from the sun or geothermal sources is usually necessary, but the time scale for their depletion is so long that these are considered to be renewable. Likewise, input resources, such as clean water, nitrogen, or phosphorus, can be made renewable if they are recycled. Sustainable designs are very much desired compared to nonsustainable designs because they can be operated indefinitely without requiring the need for remedial actions later on.

18.8 RESISTANCE DEVELOPMENT

Living things adjust to their environments. If the environments are made to be severe enough to eliminate particular organisms, then resistance to these environments is likely to arise. Such is the case for antibiotics, herbicides, fungicides, and insecticides. Resistance to elimination measures is a real issue for some biological engineering designs, and it is often the case that resistance development can be delayed more easily for measures that are less effective than for those that are more effective.

18.8.1 Refuge Plots

One mistake that is easy for a biological engineer to make is to aim for perfection in his or her designs. This includes perfect elimination of unwanted organisms. However, management and control, not total elimination, is the key to a successful biological strategy. Biocontrol can be achieved through the application of one or more living natural enemies, parasites, or predators, or through the recruitment of natural tendencies, none of which are absolutely effective.

Rather than try for a complete and total knockout of the offender, a better solution may be, and usually is, one that establishes a dominance of the favored over the unfavored individuals. Thus, the ideal pesticide is not one that eliminates all individuals of a problem pest; it is the one that shifts the balance back in favor of natural enemies. The ideal antibiotic is not the one that cures the disease 100% of the time; it is the one that weakens disease organisms but does not select for antibiotic

immunity. The ideal chemotoxic anticancer drug is not the one that kills all rapidly growing cells; it is the one that favors effective immune system response.

There have been many modern incidences of invasive pests, and one strategy for dealing with them is to discover natural enemies that can bring invasive pests back into natural balance. We know that in order for these natural enemies to continue to be effective, a small population of pests must be maintained. The result is not elimination of the pests but a balance that can be tolerated.

Bacillus thurengiensis (Bt) corn is a genetically modified grain that is poisonous to *Lepidoptera* larvae, such as corn earworm. This pest used to be very destructive to corn yields, but since Bt corn has been grown, corn yields have increased greatly, with the additional benefit that chemical pesticides are no longer needed to control corn earworm. Bt corn is so good that farmers want to plant nothing else. Yet, 100% of a corn crop that is Bt corn would ultimately lead to corn earworm insects resistant to the protection of the Bt gene; Bt corn would no longer be effective.

Farmers who plant Bt corn are required to plant non-Bt corn as 5%–15% of their corn crops. These are called *refuge plots.* Refuge plots reduce the reproductive pressure for all corn earworm insects to develop Bt resistance. With refuge plots, any Bt-resistant insects have ample opportunity to mate with nonresistant insects, thus diluting resistance genomes and reducing the possibility that resistance will be passed on to the next insect generation.

The concept of refuge plots should be known by all biological engineers and be a candidate for application to many other situations. Not all household locations need to be spotlessly clean, and not all hands need to be disinfected. Not all defective genes need to be eliminated, and not all microbial infections need to be treated with the most powerful antibiotics. Imagine, if you will, that methicillin-resistant *S. aureus* (MRSA) may not have existed if antibiotics had not been so generally used. Some staph patients could have fought the infection without the use of powerful antibiotics, perhaps with the help of some probiotics, and acted as refuge plots for nonresistant staph bacteria. *S. aureus* bacteria are omnipresent on human skin but are kept from becoming a problem because of resource competition from other bacteria also on the skin. These other bacteria are the natural enemies of staph that we could have exploited as part of our refuge plot strategy.

Biological engineers should appreciate the value of natural mechanisms and work with them rather than trying to impose complete domination. Total control of the entire biological system is not, nor ever will be, a possibility for a biological engineering solution. Balance, not perfection, is the key to successful designs.

18.8.2 Redundancy

Biological scientists have made many impressive discoveries, and these can often be used as mechanisms to solve some puzzle needing fixing. Advances made in knowledge about genetics, behaviors, or toxins have been foundational for new methods and strategies to control pests, reduce disease, or increase yields. However, these seminal advancements have usually come one at a time, after much effort and investment, and unfortunately, they are then used one at a time to solve some problem of importance.

Redundancy is the hallmark of biological response. Whether the problem is pestilence, disease, predators, or environmental challenges, living things react to these affronts with multiple responses. The immune system is a great example of this, depending on not just one but a whole host of means to thwart challengers to health and survival. It needs to be thus, because the biological threats themselves are constantly changing and attempting to nullify or avoid immune responses. The result is a dynamic, a biological parry and thrust, that rewards the strong and sacrifices the weak. Control of the target over the challenger is never totally achieved, but the target survives as long as it can, and that, in itself, is biological victory.

Biological engineers have all too often depended upon unidimensional solutions to solve their problems. These remedies have included incorporation of individual genes, dependence on pesticides with one action mechanism, and saturation with toxins differentially poisonous to pathogens

over hosts. The results are genetically modified crops, favored antibiotics, anticancer drugs, and overuse of antiseptics. It is not that these solutions are bad, because they are not, but they do not take into account that single mechanisms have not proven to be long-term solutions to problems. Pests can overcome single gene protections, microbes develop means to overcome antibiotics, cancers can survive drugs, and no antiseptic is guaranteed to kill all unwanted organisms. Overuse of systemic antibiotics may wreak havoc with the natural flora of the gut and impair digestion to the detriment of the host. What one gets when one depends on a single magic bullet is a temporary victory at best.

Agricultural fungicides are very important to protect fruit, grain, and vegetable crops from infections that could destroy them. The most effective fungicides are those with single modes of action. These are also the fungicides that promote disease resistance. Fungicide manufacturers are beginning to package these very effective single-mode pesticides with broad-spectrum pesticides. Any disease that could develop resistance to the single-mode fungicide is killed by the broad-spectrum fungicide. The second fungicide acts as the refuge plot for the first fungicide.

18.9 INFORMATION SOURCES

Information relevant to a design involving biological systems can be found in numerous places. Most engineering and biology societies have some interest in portions of the biological spectrum and have information available in journals, white papers, technical bulletins, and web expositions. It is likely, however, that all necessary information is not easily available. Nor is it likely that the information that one seeks appears all in one place, unless a similar design has been done before. Help can be obtained from society standards, biology textbooks, and experts in the field.

18.10 USEFUL TECHNIQUES

18.10.1 Scaling

One of the earliest forms of prediction in biology was the use of scaling factors, those proportions, based on morphology, that can be used to extend general knowledge about one creature to another. There are similarities in nature, and these are often caused by physical or chemical requirements that must be met by all creatures large and small.

Scaling relations can be very important in the engineering design process. One difference between an engineering design and a complete guess about what will happen is that the engineering design incorporates the best and most specific prediction based on available facts. This usually involves a calculation step to yield quantitative predictions. It may be that specific quantitative information about a particular characteristic of some species cannot be found easily. Short of performing experiments and making your own measurements, useful information can often be obtained from scaling relationships among similar organisms. Thus, answers to questions about food and oxygen requirements, waste and carbon dioxide production, natural densities, organ masses, locomotion speed, and life cycle times can all be predicted based on scaling relationships. Engineering related to biology often has a need to know such information. Designs based upon these predictions have a much better chance of success than less enlightened guesses.

Allometry is defined as the change of proportions with increase in size of a single species or between adults of related groups. Allometric relations only exist when there is similarity of structure and function between BUs of different size. If completely different mechanisms are involved (for example, locomotion of bacteria compared to horses), then no allometric relationship would be expected.

There appear to be universal biological principles at work in scaling relationships, although the natures of these principles have not yet been fully explored. Allometric relationships among very divergent species seem to be scaled with body mass to some simple multiple of one-quarter power ($m^{1/4}$). Thus,

Leaf area of trees $\propto m^{3/4}$
Radii of mammalian aortas and radii of tree trunks $\propto m^{3/8}$
Circulation time of mammal blood and of tree sap; cycle time of respiratory, cardiac, gestation, postembryonic development; life span $\propto m^{1/4}$
Biological rates, including mammalian heart rate and respiration rate $\propto m^{-1/4}$

Natural selection seems to have led to an economy of design of structures and functions so that they just meet maximum demands. Any greater capacity would be biologically uneconomical. If evolution results in allometric relationships among BUs, then it is only because the benefit-to-cost ratio of the function in question has been optimized.

Another way to think of allometry is to consider that if organisms do *not* change their form as they change in size, their function *is* altered, and such functional shifts might be a source of evolutionary innovation.

There are scale-invariant features of biological tissues, such as bone strength, wood strength, or maximum muscle stress, which require size-dependent changes in other features. These changes may be sizes of limbs or muscle masses or may be changes in posture and mechanical advantage. A more upright posture puts less bending stress on a limb by reducing the moment arm. Larger plants and animals may scale according to strength, but smaller plants and animals may scale according to stiffness: very slender elements can bend, thus putting associated muscles at a disadvantage.

18.10.2 Directed Evolution

Evolutionary principles can be used as a design paradigm. Begin with a set of specifications for performance of the final product and a means to quantify progress toward the specification goal. Next, define the starting point or configuration of the product. Then make random changes in the product while measuring how much closer to the final specification each permutation is. If the change improves the product, keep it. If the change does not, then discard it and try again.

This system can be computerized and has been used to create hundreds of inventions. This system automatically mutates a single detail of the product and distributes product characteristics to two parent products. It then mates the two parents to produce offspring. If one child is closer to the ideal than the others, it alone is retained, and its siblings are eliminated. The process of mutation, distribution, mating, and selection repeats until the product comes close enough to the specifications to be acceptable or until no further improvement is possible.

Directed evolution can be used at a microscopic scale to improve enzyme function and has been used to improve the efficiency of artificial enzymes created by computational modeling. An enzyme was designed to remove a hydrogen ion from a carbon atom as part of an organic compound. No such enzyme existed in nature. In order to respond to evolutionary methods, there must be some amount of functionality at the start. Random mutagenesis in the designed enzyme molecules and selection of those that demonstrated improved functionality resulted in a final enzyme 200 times as effective as the enzyme at the beginning. Directed evolution has also been used on a large scale to design efficient buildings and microwave antennas.

Much of technology develops in a similar fashion, except, perhaps, that the step of deliberately introducing random changes is not explicitly taken. Technology often starts with an idea that is developed using engineering principles. Thereafter, technological progress is made empirically, which means that improvement information comes from testing or use of the product. Empirical improvements derive quite often from trial-and-error, serendipitous, or practical observations, and not from application of basic engineering principles.

There is an analogy that can be drawn among the processes of technological innovation and development, the scientific method, and biological evolution and natural selection. Each of these involves a recurring loop with a starting point, testing, and discrimination against unsuccessful

variants. The results are better products or processes, better information, or more successful living beings.

In a sense, traditional breeding programs could be called directed evolution as well, except that those programs are not usually computer-centric or as automatically random as the directed evolution process described previously. In traditional breeding programs, the breeder begins with a set of goals in mind and selects plants, animals, or microbes that demonstrate progress toward those goals. This kind of activity has been going on for thousands of years and has resulted in many different breeds of dogs, livestock, fruits, vegetables, flowering plants, and specifically useful microbes, such as different wine yeasts or cheese bacteria.

18.11 REGULATIONS AND STANDARDS

18.11.1 Regulations

Regulations are rules issued by the government that have the authority of law. Applicable regulations must be followed in any engineering design, whether it includes living things or not. With such a broad range of possible biological engineering design applications, there are possibly many regulations that the biological engineer needs to be made aware of. Failure to conform to these regulations can result in criminal prosecution. In many cases, necessary regulatory compliance adds to the cost of the design.

18.11.2 Standards

Standards are agreements on best practices, usually made as a result of extended conversations among interested parties. Represented in these conversations can be industry, government, professional groups, and the lay public. Standards are often drafted and redrafted until all interested parties can agree on their wording, and not until there is total agreement. Standards can be drafted for best practices, to standardize parts or protocols, or to guide procedures from among many possible choices.

Standards do not have the weight of law. Designs that do not conform to industry or government standards are legal but, if challenged in court, can result in an adverse judgment if a design results in harm to something or somebody.

18.11.3 Agencies with Relevant Regulations or Standards

Biological engineering designs may involve living things on many different levels and in many different ways, so there is not just one set of standards or regulations that a biological engineer must investigate. In the United States, there are many different agencies that should be consulted. For instance, the U.S. Environmental Protection Agency (U.S. EPA) has a mission to protect human health and the environment. Under the Clean Water Act; Clean Air Act; Federal Insecticide, Fungicide, and Rodenticide Act; and Food Quality Protection Act, the U.S. EPA has broad powers of approval and regulation. The U.S. EPA approves and enforces pesticide usage and clean water and clean air regulations, and requires environmental impact studies to be performed before a construction project or other design with environmental implications can begin.

Not all environmental designs are part of the jurisdiction of the U.S. EPA. When wetlands are involved, the U.S. Army Corps of Engineers is the agency to consult. Endangered species are the interest of the U.S. Fish and Wildlife Service. The U.S. Food and Drug Administration (U.S. FDA) partners with the U.S. EPA in dealing with pesticides and food safety. Food safety inspections are the responsibility of U.S. FDA and the U.S. Department of Agriculture (USDA). Workplace environmental hazards are regulated by the U.S. Occupational Safety and Health Administration (U.S. OSHA), unless mining is involved, in which case the U.S. Mine Safety and Health Administration

(U.S. MSHA) is the governing agency. Other agencies that might have jurisdiction in a particular case are the U.S. Department of Energy, U.S. Department of Transportation, U.S. Consumer Product Safety Commission, and the Nuclear Regulatory Commission.

The U.S. FDA, USDA, and U.S. EPA have joint responsibility for overseeing the environmental release of genetically modified organisms (GMOs), usually for commercial purposes. The U.S. National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules deals mainly with experimentation with organisms produced by synthetic biology.

Other regulations are administered largely locally. Many environmental regulations are locally determined, usually at the state level. State environmental standards are often more strict than national environmental standards. Local health departments have regulations involving food preparation and waste disposal, and these regulations can vary from location to location.

Many professional and technical societies have a standards-producing activity. The Institute of Electrical and Electronics Engineers (IEEEs) has standards for electronic and computer devices, and the American Society of Mechanical Engineers (ASMEs) has standards for mechanical and heat transfer devices. The American Society for Agricultural and Biological Engineers (ASABEs) has standards for agricultural implements and use. The American Society for Testing and Materials (ASTMs) has standards for various materials and devices. Other standards are available from societies representing specific industries, such as automobiles, petroleum, biomaterials, and medical care. In the United States, the American National Standards Institute (ANSI) oversees the creation, promulgation, and use of thousands of norms and guidelines that directly impact businesses in nearly every sector, from acoustical devices to construction equipment, from dairy and livestock production to energy distribution, and many more. The International Standards Organization (ISO) has standards for protocols and procedures on a multinational level.

18.12 ETHICS

The ethics of treatment of other species by humans is usually denoted as *environmental ethics*, and there are many different ways to look at environmental ethics. Dealing with medical ethics, or the ethics of human-to-human relations, is not in itself simple, but dealing with the whole range of other species present in the environment opens up a very large series of assumptions, questions, and approaches to these questions. The issue of boundaries comes up: where does one draw a line separating a species or individual of that species deserving of moral consideration from one that does not?

The approaches to environmental ethics derive fundamentally from philosophy and religion. People from a Judeo-Christian background are likely to have a different view of environmental ethics than someone from a Hindu background, and both of these could possibly differ in their attitudes from a Native American. Given such a fundamental difference, there are likely to be many different extant interpretations of ethics and possible conflicts among them. Most of the ethics in Western culture were articulated and developed in the Western world. Even there, many different thoughts and values have been expressed, and these continue to change and develop over time. The point of this short discussion is that an engineer who produces designs that impact living things should be aware that the design could fail if the ethics that prevail in the location and at the time of the design are ignored.

18.12.1 Reverence for Life

Going back to the first principle of biology, the imperative for survival and reproduction, suggests a very basic ethical principle: all life is precious and should not be casually destroyed. The drive to survive and reproduce is present in the very genes of every living thing, so this principle extends down to the most basic of organisms. However, there is not a hard-and-fast definition of what constitutes life, so even this principle is open to interpretation.

18.12.2 Human Centered

Most ethical issues are related to the value of a species to human beings, and this value can be measured monetarily, emotionally, or from a utilitarian viewpoint. Thus, we can think of the value of our pets and project our morality onto them as individuals. We may care less for a whole species than for one or two representatives of that species. On the other hand, we think little of a creature we find repugnant, or even extremely negatively about an organism that causes human, animal, or plant disease. We have nearly eliminated whole species of microbes (i.e., variola, the virus causing smallpox) with celebration. We have also eliminated species of animals (i.e., carrier pigeons) with regret. The conceptual mental image of the carrier pigeon is obviously of higher value to humans than is the avatar of a smallpox virus.

Some creatures are seen as very useful to us and should be protected for that reason alone. One of the main arguments against environmental destruction is the possibility of some future benefit for humans of the species destroyed. The interconnectivity among any BU and its physical, chemical, and biological environments means that no design is ever without its broader consequences, and these need to be carefully measured.

From this, we can see that many environmental ethical decisions are made along a concept of concentric rings, where the most ethical protection is placed on those creatures of most value to humans, with less and less consideration given to creatures far outside the inner circle.

18.12.3 Sentience

It has become apparent that self-awareness is possessed by degrees. Some creatures are more sentient than others, and those that are more aware of themselves and their relations to others are accorded more ethical consideration.

18.12.4 Suffering

Whether all living things can suffer pain is not known. However, people project onto other creatures their own feelings of suffering. It is clear that certain animals feel physical pain and suffering because they react to pain in recognizable ways (cries, writhing, avoidance, etc.). Whether microbes and plants feel pain is questionable. Certainly, all living things can sense their environments; whether this translates into pain is not known. Nevertheless, it is generally accepted that undue suffering is to be avoided whenever another creature is involved in a design or test. Therefore, certain drug tests, medical device tests, environmental modifications, or agricultural operations are to be avoided if there are means to the same end that cause less pain, suffering, or distress. Euthanization of animals must be done with as little pain and suffering as possible.

Mental suffering is also a possibility for animals exhibiting some degree of sentience. Boredom can affect the physical health of animals lacking mental stimulation. Individual isolation can lead to self-inflicted physical or psychological wounds and so should be avoided. The ethical course of action is to provide interesting environments (including toys, other animals, television, and sufficient space) for these animals.

18.12.5 Animal Rights

Of current interest are the rights that are attributed to animals. Some would argue that these rights are inherent in the basic nature of these animals; others might argue that they are conferred by humans who are in control. Animal rights, as an issue, is especially important to the use of animals for testing; for animals used for military purposes (where, for example, the animals might deliver explosives to a remote location and then are destroyed when the explosives are detonated); or for agricultural livestock production. Some groups object on ethical grounds to these uses of animals.

Animals kept in housing facilities, on farms, in zoos, or as pets, must be treated with some respect. Some basic rights that have been articulated for these animals are the freedom to do the following:

1. Turn around
2. Groom
3. Get up
4. Lie down
5. Stretch limbs freely

Note that there is no agreement on whether wild animals have a right to exist in their natural environment.

There is no hard line to be drawn here, although vertebrate animals are given rights not given to invertebrate animals. Protocols for tests conducted with vertebrates in the United States and other places are required to be reviewed by animal use committees, whereas no such requirement exists for the use of invertebrates. This requirement has the force of law.

18.12.6 DNA Modification

There are restrictions on DNA modification in humans; at this point, at least, no DNA modification can be made to the germ cell line of a human. No such restriction is in place for other species, so insertion of genes to protect against diseases or pests, or to confer the ability to produce products useful for humans, can and have been introduced into the reproductive germ lines of animals, plants, and microbes without significant moral or ethical objection. The major objection to genetically modified food plants by recombinant methods is questionable safety, with some concern for environmental effects (whether or not each of these is true). The ethics of DNA modification are likely to change considerably as modified products become more and more familiar.

18.12.7 Cloning

Likewise, cloning of animals for testing and food purposes has been accomplished without too much ethical or moral objection. Test animals genetically modified to exhibit human infirmities have been cloned in order to provide uniform test subjects for possible treatments. Livestock have been cloned to provide uniform cuts of high-quality meat. There have been almost no objections to these. The place where animal cloning has raised ethical discussion is in the cloning of animals to produce replacement parts for humans. The objections here center around (1) the blatant exploitation of another species solely for human convenience or comfort and not for immediate survival needs (such as food to eat; the same objection extends to the use of animals solely for their fur) and (2) the possible introduction of foreign pathogens endemic to the animal species into the human population through the xenotransplantation of replacement organs.

Animal cloning requires that the DNA of a donor be inserted into the nucleus of an egg cell of the recipient. Nuclear DNA of the eukaryotic clone is thus identical with the DNA of the donor. This should make the clone identical to the donor except for two things: (1) the recipient cell also contains extranuclear mitochondria, each with its own DNA identical to that of the recipient, not the donor, and (2) the environment of the developing clone cannot be the same as the environment of the donor, so epigenetic changes can cause the same genes to be expressed in different ways. Practically speaking, most clones produced to date have had physical abnormalities, including shortened telomeres starting at the length of the recipient cell, which have limited their usefulness, but research to produce better clones progresses.

Cloning plants, microbes, and some lower-level animals (such as flatworms) can be easily done without nuclear DNA transfer and has been common for many years, not only without objection but

also with encouragement. Vegetative (asexual) reproduction of plants, for instance, is important for food production in commercial quantities and is recognizable with patent protection in the United States.

18.12.8 Synthetic Biology

Synthetic biology poses a severe ethical problem because the organism DNA manipulation is so extreme, the technique is so new, and so little is known about the results of drastic changes in genetic regulation. In addition, creating new life forms taps into our inner instincts about what is natural and what is our relationship to the natural world. Synthetic biology results in entire organisms that have never been found in nature and serve precisely specified human purposes. There is concern, even fear, that these organisms could cause disasters never before found in nature if they were to escape into the surrounding environment. Questions have been raised about public health, environmental contamination, and even deliberate misuse or weaponry. On the other hand are the promises of more effective medicines, intelligent tumor-seeking bacteria, and cheap biofuels that can result from organisms that are designed specifically to provide solutions to current needs. The ethical response to the challenge of synthetic biology is to look at risk–benefit ratios for specific cases and decide on proper responses once sufficient safeguards are in place.

18.13 BIOLOGICAL ENGINEERING DESIGN EXAMPLES

The following are design problems given in the classroom. They are meant to illustrate the range of subjects that can be expected to require engineering expertise. They also demonstrate the spectrum of knowledge that is required to solve each of these real-life examples. As with most engineering problems, there is not one single answer for each problem.

18.13.1 Groundwater System Contaminated with Methyl Tert-Butyl Ether and Petroleum Hydrocarbons

Corrosion in an underground pipeline carrying jet fuel to a military facility caused it to develop small holes, resulting in extensive soil and groundwater contamination. Methyl tert-butyl ether (MTBE) was added to the jet fuel as an oxygenate and consequently was a key contaminant in the area surrounding the release. The most heavily contaminated soil was excavated and removed from the site. However, the concentration of MTBE in water obtained from sampling wells closest to the contamination site ranged from 110 to 13,500 μg/L, and state regulations required additional remediation of the groundwater and soil left in place to achieve a groundwater MTBE concentration of 200 μg/L. Approximately 1.5 m of low-permeability silty clay covered with turf was underlain by a sandy layer. Groundwater was located in the sand and completely saturated the entire sandy layer during the rainy season (winter and spring). However, during the dry season (summer and fall), the water table moved down to 2.5–3.0 m below the surface, leaving 1.0–1.5 m unsaturated sand below the clay layer.

The proposed remediation strategy involves in situ air sparging (IAS) and soil vapor extraction (SVE) in conjunction with in situ bioremediation. IAS/SVE was selected as a treatment approach because it directly removes petroleum hydrocarbon and MTBE mass, and the oxygen added to the groundwater and unsaturated soil stimulates aerobic biodegradation of the contaminants. In addition, the natural water table at the site needed to be lowered in order to enhance the extraction of contaminants in the saturated zone. Although this could be accomplished by pumping with a groundwater extraction well, this would generate a large volume of water that would require treatment aboveground. Instead, it was decided that the injection of pressurized air during air sparging would be used to lower the water table. Because the low-permeability clay layer overlaid

the sand at the site, short-circuiting of the injected air into the atmosphere was not expected to be a problem.

Based on previous experience with similar sites, a total of 44 wells will be constructed on site. Each well will be connected to both a vacuum extraction and air injection manifold and therefore can function as either an air injection or vacuum extraction well. The wells will be placed 9 m apart in rows that are parallel to the pipeline and 6 m apart. The wells will be made of 10 cm schedule 40 polyvinyl chloride (PVC) pipe and have slotted sections extending from 1.2 to 4.3 m below the surface.

Design the air injection system and give recommendations for types and locations of monitoring gauges.

Solution approach:

This is a simple pumping problem involving compressible air. The resistances of the pipes and soil must be determined from typical data available in various references or the Internet. Before calculations can be started, decisions must be made about the pipe layout. Are pumps to be located at each well, or will there be a central pump location? The central location is probably the most economical. Necessary pump specifications include capacity, discharge pressure (determined from resistances and flow rates), and type (centrifugal, piston, regenerative, or other). The complete solution will include layout drawings, a list of materials, and pump specifications.

18.13.2 Minimizing Damage to a Salt Marsh

A New England salt marsh is a harsh and diverse environment for both plants and animals. The low marsh area from beyond the water's edge to the mean high tide level is dominated by cordgrass, ribbed mussels, and fiddler crabs. The high marsh area, from the low marsh to the level of the monthly extreme high tides, has salt meadow hay in the lower part and black rush in the higher. A combination of competition and predation keeps this marsh in ecological stable balance.

Although the low marsh seems to be a more difficult environment because its soil is waterlogged and constantly eroded by the tide, the high marsh is actually more difficult to restabilize after a disturbance. Bare areas in the high marsh allow sunlight to heat the exposed soil surface and to evaporate moisture. The soil becomes more saline. The soil salinity in large bare patches between salt meadow hay and black rush can become 30 times that under dense perennial vegetation. Closer to the sea, frequent flooding limits the accumulation of surface salt, and further into the black rush, rainwater dilutes any salty soil. Hypersaline soil prevents the germination of many seeds and slows marsh healing.

A client of yours, Investocorp, has a planned construction project that requires access across a portion of a high marsh in Rhode Island. Although repairing the damage from the traffic will not require more than 1 month to complete, vegetation in bare areas left in the marsh could take years to become reestablished. The company cannot afford the regulatory and public-relations costs of such destruction. Investocorp is asking you to perform a feasibility study using some kind of cover or coating on the high marsh areas damaged by traffic to allow quick reestablishment of native vegetation. Consider, in your report, (1) ways to minimize traffic damage, (2) the rate at which moisture is lost from the ground on bare earth compared to vegetated earth, and (3) how to provide an adequate local environment to germinate salt hay seed.

Solution approach:

To solve this problem requires a lot of research on salt marshes and vegetation. There will not be only one acceptable solution, although some solutions might be better than others. Each possible solution will probably involve compromises. The overall problem can be considered in parts; there is the compaction of the soil, which is probably not too extreme during high tide when soil pores are filled with water, and the effects of denuding due to mechanical damage to the plants as vehicles run over them. An acceptable solution probably involves some plant protection as well as scheduling of traffic across the marsh.

18.13.3 Freezing Hamburger

Fedbeef, Inc. supplies frozen hamburger to public schools under the federal government's lunch program. The hamburger begins as beef chunks that are prechilled in a ribbon mixer that is sealed and injected with cold CO_2 until the meat is –2°C. The meat is on the verge of freezing. The chunks are then ground cold to prevent smearing.

After grinding, the hamburger is packed in 2.3-kg-capacity polyethylene bags, and the bags placed into corrugated cardboard cases containing 227 kg of meat (net). The cases are then stacked on pallets, and the pallets are stacked four high.

Freezing is performed in a freezer 21 m long × 11 m wide × 8 m high. The meat must be completely frozen within 72 h by federal regulation.

Design the freezer, including the following:

1. The temperature of freezer air supply
2. The volume flow rate of air
3. The capacity of the refrigeration unit

Other information:

Warehouse walls are 30 cm thick filled with fiberglass insulation. The roof is also 30 cm thick with an airspace above the insulation and below the covering roof to allow free flow of ambient air. The floor is insulated with 15 cm of insulation.

Hamburger is 30% fat, 70% lean.

Normal procedure is to use a temperature of –30° to –40°C to freeze.

Clearance between the walls and pallets is 46–61 cm. Pallets are put in racks holding 4 pallets high and 3 pallets deep.

Box dimensions are 52 × 40 × 15 cm. Cardboard wall thickness is about 1.5 mm. There are no holes in the cartons. There are five boxes per layer, and the wall is five layers high. Spacers allow 4 cm between the layers, and boxes are approximately 7 cm apart. Height on the pallet is about 1 m.

Solution approach:

Physical properties (thermal conductivity, specific heat, density, water content) of ground beef must be approximated. This can be done by looking up properties of the fat and lean meat and calculating the resulting properties based on mass fraction. The percentages of fat and lean meat given here are traditionally given on a volume basis, so this must be converted to masses. Based on the water content, freezing point depression temperature may be calculated to approximate the freezing temperature of the ground beef. The problem specifies the normal air temperature to freeze the hamburger patties. Freezing times of the palletized hamburger patties should be checked to assure that they freeze in the legally required time. For this, the convection coefficient of the air in the warehouse must be calculated. Heisler charts can be of assistance for freezing times. A heat balance on the warehouse gives the heat absorbed from the hamburger and heat absorbed through the floor, walls, and roof. Insulation values for cardboard, fiberglass insulation, and building materials must be looked up in tables. Do not forget the convection coefficients inside and outside the walls and roof when calculating heat transfer. Rate of airflow can be determined from the required convection coefficient to freeze the hamburger. The capacity of the refrigeration unit can be obtained from the heat balance on the warehouse, including the inefficiency of the unit.

18.13.4 Drying Yew Materials

Brimstone, Mire, and Squish (BMS) is a pharmaceutical firm that intends to become a major supplier of Taxol, the alkaloid that has proven to be very effective against ovarian and breast cancers. Taxol has been obtained from the dried bark of the Pacific yew, *Taxus brevifolia*, but a more reliable

and ecologically sensitive source of Taxol can be obtained by extraction from dried clippings of the cultivated yew variety *Taxus x media* Hicksii.

Annual demand of Taxol in the United States is expected to exceed 20,000–25,000 kg. Approximately 250,000,000 kg of fresh needles, or slightly more mass of fresh clippings, is required to satisfy this Taxol demand.

BMS has contracted with Weimarhowsat, Inc. to grow the yews in plantations. The clippings are to be harvested mechanically and placed in driers to be dried in thin layers using air at 40–50°C. Dried clippings will be stored until Taxol extraction, for a time period of up to 6 months.

Design a pilot-scale drying facility to handle at least 1,000,000 kg of needles and twigs per year. Include the following in your design:

1. The layout of the drier
2. Air handling arrangements
3. Product handling arrangements
4. Heating requirements

Solution approach:

Thin-layer drying is characterized by a relatively constant moisture content across the thickness of the layer and thus is somewhat simpler to design than is thick-layer drying. Physical properties (thermal conductivity, specific heat, density, moisture content) of the yew wood must be looked up. The drying process depends on a mass balance on the yew material. The yew chips can probably be considered to be a packed bed with air blowing through it. Psychrometric conditions (dry bulb temperature, relative humidity) of the incoming air must be assumed and justified. These psychrometric properties can be converted into others using a psychrometric chart. The air will undoubtedly need to be heated. The temperature rise can be assumed and then checked later. From the relative humidity of the heated air, an equilibrium moisture content of the yew chips can be found. A rate of air movement must be determined or assumed. Once that is done, a mass balance gives the rate of moisture removal. The required heat source can then be calculated from the rate of air movement and the assumed temperature rise of the air. Some heat will be lost outside the dryer, so the heater capacity needs to be increased somewhat. A fan needs to be specified (capacity, discharge pressure, type) to supply the required amount of air. The discharge pressure will depend mostly on the pressure drop in the layer of chips, with some additional resistance of the piping. Use Bernoulli's equation to determine pressure. The dryer layout and product handling arrangements are made using engineering judgment and precedent.

18.13.5 Cystic Fibrosis Gene Delivery

Gen Vec proposes a system to deliver a cystic fibrosis (CF) gene to the epithelium of CF patients. The gene will be incorporated in an adenovirus vector and is to be administered to the upper-airway epithelial cells. The goal is to reach 1% of the epithelial cells, each of which has an exposed diameter of 10 μm. To do this, a total of 10^9–10^{10} particles must be delivered to the patient per treatment.

One of the main symptoms in CF is a very viscous mucous that accumulates on the respiratory airway walls. Whereas the thickness of mucous in normal patients is about 5–10 μm, the mucosal thickness in CF patients is 100–500 μm. CF mucous is about 10 times more viscous than normal mucous.

Beating cilia in the airway linings normally move mucous toward the mouth, where it can be expelled. While the cilia may still beat in CF patients, the extra-thick mucous does not move well. This mucous accumulation causes episodes of severe respiratory distress.

Normal treatment for CF patients is to lie on their stomachs, with their heads lower than their bodies, while their backs are pounded repetitively to loosen the mucous and bring it to their mouths,

where it can be expectorated. Such treatments have been responsible for lengthening expected lifetimes from the teens to the thirties.

In this proposed treatment, the CF gene will be introduced to solve the problem at its source. Particles of viruses in liquid will be generated as an aerosol while the patient breathes. Diameter of the particles is to be 1–5 μm to assure impact in the target area of the respiratory system. Once the particles impact the mucous, they must move across the mucous layer by diffusion to reach epithelial cells. When they reach the cells, an assumption of 100% effectiveness of gene delivery can be made, although this information is not really known. Your problem, then, is to evaluate this proposal for technical feasibility. Be sure to consider both the delivery of the particles into the respiratory system and the diffusion of particles across the mucous layer. Make any recommendations that you can to improve the efficiency of the technique.

Solution approach:

First, it has to be noted that no one has as yet solved this problem, so it can be a real challenge for the student to design an acceptable system. That said, this problem can be approached as a mass transfer problem; if the viruses can be delivered to the epithelial cells lining the airways, it can be assumed that the viruses will penetrate the cell walls and deliver the necessary gene. Physical properties (mass diffusivity, density) of the mucous must be looked up. This may require some approximation. Then Fick's law can be used to calculate the rate of particle movement from the lumen of the airways to the lining surface. Once that is done, a means to supply the required concentration of viruses to the inhaled air can be devised. Not all viruses impact the mucous; some will be exhausted by the exhaled breath.

EXERCISES

1. *Encephalogram Classification.* Frequencies of electroencephalograms (EEGs) can be used to indicate states of alertness. Slow alpha waves (8–12 Hz) are produced during wakeful relaxation; midfrequency beta waves (12–30 Hz) are produced in awake, active concentration; and high-frequency gamma waves (25–100 Hz), which appear much as noise, are a signal of alertness.

EEG signals are obtained from electrodes placed on the surface of the scalp. These electrodes are similar to electrocardiogram (ECG) electrodes. That is, they detect small (10–100 μv) signals with very low current.

An instrument that classifies EEG signals into alpha, beta, and gamma regimes would be useful for neurophysiologists working with both humans and animals. Design, build, and test such a device.

Specifications:

Input voltages: 1 mv max
Input impedance: 500 kΩ or greater
Output indicators: seven-segment display showing A, B, or Γ
Display reset: once every 30 s; the display should go dark during reset

2. *Artificial Heart Testing.* Careful development and testing of artificial hearts and left ventricular assist devices requires a means for in vitro testing. Using a mechanical model of the human circulatory system would enable pump testing for satisfactory performance, reliability, control system development, and circulatory pathology simulation. The use of the mechanical model is both ethically and legally required before the pumps can be installed in either animals or humans.

A mechanical model must have these characteristics:

1. The system must provide an accurate analog of the cardiovascular system from an overall hydraulic impedance standpoint. That is, it must include realistic resistance, compliance, and inertance values.

2. The system must have readily adjustable resistance and compliance elements so that various physiological conditions can be simulated.
3. The system must be able to simulate, from a configuration standpoint, the in vivo attachment and environment of the device to be tested.
4. The system must be of such a design that an analytical model can be developed to establish the reliability of the mock loop.
5. The system must be easy to operate.

Design a mechanical analog circulatory system for both pulmonary and systemic circulations for pumps delivering cardiac outputs of 2–6 L/min at rates of 70 pulses/min.

3. *Hypothermia System for Veterinary Medicine Clinics.* Get 'Em Pooch Associates Veterinary Medicine Clinic is a private veterinary clinic. We handle both domestic and farm animals. When performing cardiac surgery, it is sometimes desired to reduce the patient's body temperature in order to slow metabolism. This procedure is called induced hypothermia. We need a system that will decrease the patient's core temperature, hold this temperature during surgery, and then increase the temperature to normal. The system should be capable of handling any size animal from cats and rabbits to cows and horses. The system should be composed of materials that are biocompatible and readily available.

4. *Hazardous Materials Protective Suit.* Super Fund, Inc. is a small company involved in the design and manufacture of protective equipment to be used in the cleanup of toxic materials. There is a new line of protective suits that needs to be designed for the company. As a biological engineer, you are being hired to design the new suits.

Required specifications are as follows:

1. Suits completely impermeable to liquids, gases, and vapors.
2. Air supplied with hoses to a central heating/cooling unit located up to 10 m away from the position of the person working in the suit.
3. Up to three suits to be operated from one heating/cooling unit.
4. Suit is to be worn for up to 4 h at a time.
5. Suit should be able to be worn in a temperature range of −10°C to 35°C, in the sun or shade.
6. Suits should be able to be cleaned of contaminants and resist abrasion during operation.

Work with our clothing people and recommend specifications for the central heating/cooling unit. These specifications must include the following:

1. Rate of airflow
2. Charcoal filter capacity
3. Maximum heating and cooling capacity
4. Type and size of power to run the unit
5. Recommendations on techniques to control suit air for desired environmental condition

5. *Packing Spices.* Mickey Mack is a Hunt Valley, Maryland spice manufacturer. Mickey Mack has just received a new contract to supply 20 kg packages of selected spices to Regresso Foods for their line of Italian foods. Whereas Mickey Mack has much experience with the supply of spices for the home market, this contract represents a new market for our product. We need a new package to be designed to contain 20 kg of spices. The package must be inexpensive, rugged, and protective of volatile components present in our spices. Please design such a package.

6. *Ventilation System for Mouse Rearing.* Jackson Labs in Bar Harbor, ME raises laboratory mice used for medical purposes. Their special JAX mouse, and mouse models specifically genetically engineered for heart disease, cancer, CF, and obesity, are world famous. Jackson Labs raises about 3 million mice per year and ships about 50,000 mice per week to laboratories all around the world.

Mice are raised in mouse cages with 40,000 mice per room. There are 10 mouse production rooms. Each cage is individually ventilated with 60 air changes per hour, and, overall, each room is supplied with at least the minimum of 10 air changes per hour (as specified by animal production standards). Rooms are to be maintained at 21°C ± 0.6°C and 45% RH ± 5%.

Female mice are maintained on a 7-month breeding cycle, during which they produce four to six litters. They are kept in custom-designed polycarbonate cages 25 × 15 × 30 cm with wood shavings on the bottom. Because mice are physically active at night, there is a high particulate loading in the room air that must be removed with a high efficiency particulate air (HEPA) filter.

The present ventilation system is being replaced, and we need you to design a new system for us. We especially need you to recommend the following:

1. Heating/cooling capacities
2. Fan specifications (capacity, pressure, power)
3. Heat recovery systems to improve heating/cooling efficiency

Other information:
Heat production/mouse = 0.47 W
Air supplied at 16°C, pick up 5°C in room
Pressure for room (need positive pressure to reduce bacterial contamination): 15 ± 2.5 N/m^2

7. *Mayonnaise Processing.* Hellperson's Inc. of Englewood Cliffs, NJ wants to expand its mayonnaise production capacity by adding another processing line. The line is to be built inside a new building, and the building layout will determine the type of structure built.

Mayonnaise is made from the following:

Vegetable oil	80%
Egg yolk	8.0%
Mustard flour	0.5%
Vinegar, 100 grain	3.0%
Water	6.0%
Salt	0.5%
Sugar	2.0%

The flow sheet for mayonnaise manufacture shows the sequence of operations.

The premixer is an agitated jacketed kettle of about 1900 L capacity. Since this is a batch operation, two premixers could be used to provide a continuous supply of mayonnaise mix to the pump and colloid mill. A funnel should be located just prior to the colloid mill to assure that air is not introduced into the mill. A minimum pressure of 30 kN/m^2 must be provided in the product entering the mill. It is likely that a second pump will be needed to supply the bottom fill piston filler that fills mayonnaise jars.

The entire process must occur at a minimum of 82°C. Provisions must be made for cleaning in place at least once per day with water and caustic.

Design the processing line pumping and piping from the premixer to the filler.

8. *Bioreactor Temperature Control.* The Celligen Plus Bioreactor, manufactured by New Brunswick Scientific (Edison, NJ), can be used with the Baculovirus Expression Vector System (BEVS) for the production of a variety of products such as vaccines, enzymes, growth factors, hormones, and monoclonal antibodies. BEVS is based on constructing recombinant baculoviruses by replacing the polyhedron gene with foreign DNA and then using these viruses as vectors for the infection of insect cells. The most extensively studied baculovirus is *Autographa californica* and *Spodoptera frugiperda* Sf-9 and Sf-21, and *Trichoplusia ni* Tn-368, BTI-TN-5B1-4, or High Five are insect cell lines commonly used in the biotech industry.

The bioreactor supplies oxygen for the growing cells at a rate of 15–45 mg O_2/mg cells/h, and this requirement nearly doubles after viral infection. Other proprietary cell lines may have higher oxygen requirements yet. A large orifice ring sparger is used to keep shear rates below those most detrimental to the cells.

Continuous perfusion is used to increase the cell density by at least a factor of four. The bioreactor configuration includes a source of serum-free medium, peristaltic pump, and level control. Discharge is pumped from the reactor through a hollow fiber cartridge, where the waste is separated from the cells. The waste ends up in a waste carboy, and the cells are returned to the bioreactor. Perfusion rate varies with cell density in order to be most effective.

You are a group of engineers working in the biotech industry and plan to start your own company. Your first product is to be a temperature control system to be added to the Celligen Plus Bioreactor. Design such a system. Details of the control system need not be given, but an outline of the control system is necessary. Detail the thermal design, including means to heat or cool the bioreactor and the amounts of each needed.

9. *Mercury in Danbury, CT.* Danbury, CT has a mercury problem. At one time, there were many factories there that made felt hats. Mercury was used to soften animal pelts to make the felt, and, when the mercury bath was spent, factories just dumped it and started again. Over time, the levels of methyl mercury in the soil rose, and they are now commonly in the range of 1–315 ppm. The city wants to clean up this property and bring the mercury level to no more than 20 ppm for residential sites.

Instead of digging up the soil and treating it, the city will use genetically modified cottonwood trees to phytoremediate the site. Cottonwood trees quickly develop extensive root systems and grow quickly. It is intended that the trees will absorb the mercury and be cut down in 4–5 years before they reach reproductive age.

The trees will be supplied by Applied Phytogenetics, located near Athens, GA.

As the biological engineer consulted for this project, how long do you estimate it will take to reduce mercury levels to the desired threshold? How densely should the trees be planted? How should the trees be managed to remove the most mercury in the shortest amount of time? What should be done with the trees once they are cut?

10. *Raisin Rinse Water.* National Raisin is the second-largest processor and distributor of raisins in the United States. The 200,000 kg of raisins per day generates between 240,000 and 320,000 L/day of wastewater. Raisins have a fine coating of dust blown onto them from the sandy soil in the Central Valley of California, and this needs to be washed off before packaging.

Dust by itself could be removed from the wastewater by simple settling tanks or filters. However, when the dust is washed off the raisins, some of the sugar in the raisins also dissolves in the water. Consequently, the sugar containing wastewater has a high biological oxygen demand (BOD). Land application of high-BOD water can be expensive and requires a special permit. Municipal wastewater treatment plants charge much more (up to $50,000 per month for National Raisin) to treat high-BOD wastewater.

Removing the sugar from the wastewater by ultrafiltration is an economic solution. The clean water (permeate) can be sent to the city sewer, used for irrigation, or reused as wash water. The concentrated sugar solution (retentate) can be sold to local distilleries to make grape alcohol.

Normal raisin wash water contains 2%–4% sugar. This must be raised to a minimum of 8% sugar if the local distillery would be interested in purchasing it.

The membrane system chosen by National Raisin was the Model B1 filtration modules manufactured by PCI Membrane Systems in Cincinnati, OH. Eighty of these units will be used, and up to 120 units can be purchased to meet increased demand in the future.

We will hire you as a consulting engineer to design the system to collect raisin wash water and pump it to the filter. Then additional pumping systems must be designed to pump the retentate and permeate to holding tanks. Holding tanks must be large enough to accumulate 2 days' supply of liquid.

Additional information:

Filtration units are to be located in a newly constructed annex to the raisin-handling and washing facility. The annex is 20 m away.

Filtration units are located in parallel fluidically. Engineers should propose a configuration.

Locations of retentate and permeate holding tanks should be located separately so that the liquids in each can be handled differently.

11. *Metering Caenorhabditis elegans. Caenorhabilitis elegans* was the first multicellular eukaryote to have its entire genome sequenced. It is a 1-mm-long transparent flatworm nematode that is used for many genetic experiments.

Bioworm is a small company that grows and supplies *C. elegans* to scientific labs. They grow special worms containing the green fluorescent protein gene in muscle and nerve cells for ease in tracking genetic changes. Although *C. elegans* normally feed on bacteria, Bioworm grows them in 20 L flasks containing *C. elegans* Maintenance Medium, or CeMM for short. These flasks are inoculated with adult nematodes at a rate of 100 nematodes per milliliter. In 3 days, the flasks contain 10^6 nematodes per milliliter.

Bioworm then intends to transfer nematodes to 50 mL flasks for shipment to customers. This should be done with an automated system that mixes the contents of the 20 L flasks to assure uniform nematode density, and meters exactly 50 mL into each customer bottle, all without harming the live nematodes. Design such a system.

12. *Quagga Mussel Threat.* The Calvert Cliffs nuclear power plant draws water from the Chesapeake Bay to provide cooling of the reactor. There are two units and six pumps per unit. Each pump draws 760 m^3/min of water through a 2.74-m-diameter pipe.

Zebra mussels have recently been discovered in the Chesapeake Bay, and there is a threat of an even more competitive species, Quagga mussels, appearing in the future. They feed on small bacteria and love to colonize the interiors of water intake pipes. There, the continuous flow of water provides a steady supply of food and oxygen and carries away waste. They are also protected against predators, silt, and waves.

As the mussels line a pipe or tunnel, they disrupt water flow. A single layer of mussels is 2.5 mm thick. In extreme cases, colonies can reach 30 cm thickness. Typical thickness inside pipes is 5.0–7.5 cm.

You have been hired as a consultant to assist Constellation Energy deal with the Quagga mussel threat. Estimate the potential reduction in intake water flow should the Quagga mussels colonize the water intake pipes, and provide a possible means to avoid or overcome the expected flow reduction.

13. *Flow Cytometry.* Flow cytometry is popular for detection or separation of labeled cells. In a flow cytometer, cells are separated into droplets of carrier liquid and passed through a capillary tube.

Laser light is used to excite fluorescent dye markers on cells, and forward or backward scattered light is used to count cells and identify cells tagged with fluorochromes.

Cells are usually present in a container, and an immiscible sheath fluid flows past the usually water-based fluid containing the cells. The sheath fluid flows faster than the cell medium, thus separating droplets of cell medium. Each droplet is assumed to contain one cell.

Normal flow cytometers can count thousands of cells per second, but Beckham Spice Dickens wants to design a new flow cytometer 100 times as fast. To do this, they want to place 100 capillary tubes in parallel. Their standard capillary tubes are 30 cm long × 50 μm in diameter.

You have been hired to design the flow system for this new cytometer model. Specify all components. Remember to treat the cells gently.

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19 International Regulations and Standards

> The Lord's Prayer is 66 words, the Gettysburg Address is 286 words, and there are 1322 words in the Declaration of Independence. Yet government regulations on the sale of cabbage total 26,911 words.
>
> **David McIntosh**

The degree to which formal standards and regulations are applied to product development varies from company to company. In many cases, standards are dictated by customers or regulatory mandate. In other situations, standards are self-imposed. If formal standards do exist, assurance activity must be established to assure that they are being followed. An assessment of compliance to standards may be conducted as part of a formal technical review or by audit.

The European Commission's (EC's) program on the completion of the internal market has, as the primary objective for medical devices, to assure community-wide free circulation of products. The only means to establish such free circulation, in view of quite divergent national systems, regulations governing medical devices, and existing trade barriers, was to adopt legislation for the community, by which the health and safety of patients, users, and third persons would be ensured through a harmonized set of device-related protection requirements. Devices meeting the requirements and sold to members of the community are identified by means of a CE mark. CE stands for *Conformité Européenne*, which is French for "European Conformity."

The Active Implantable Medical Devices Directive (AIMDD) adopted by the community legislator in 1990 and the Medical Devices Directive (MDD) in 1993 cover more than 80% of medical devices for use with human beings. After a period of transition, that is, a period during which the laws implementing a directive coexist with preexisting national laws, these directives exhaustively govern the conditions for placing medical devices on the market. Through the agreements on the European Economic Area (EEA), the relevant requirements and procedures are the same for all EC member states and European Free Trade Association (EFTA) countries that belong to the EEA, an economic area comprising more than 380 million people.

19.1 DEFINITION OF A MEDICAL DEVICE

The various Medical Device Directives define a medical device as

> any instrument, appliance, apparatus, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
>
> - Diagnosis, prevention, monitoring, treatment or alleviation of disease
> - Diagnosis, monitoring, alleviation of or compensation for an injury or handicap
> - Investigation, replacement or modification of the anatomy or of a physiological process
> - Control of conception
>
> and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

One important feature of the definition is that it emphasizes the "intended use" of the device and its "principal intended action." This use of the term *intended* gives manufacturers of certain products some opportunity to include or exclude their product from the scope of the particular directive.

Another important feature of the definition is the inclusion of the term *software*. The definition of software will probably be given further interpretation but is currently interpreted to mean that (1) software intended to control the function of a device is a medical device; (2) software for patient records or other administrative purposes is not a device; (3) software that is built into a device, for example, software in an electrocardiograph monitor used to drive a display, is clearly an integral part of the medical device; and (4) a software update sold by the manufacturer, or a variation sold by a software house, is a medical device in its own right.

19.2 THE MEDICAL DEVICE DIRECTIVES

19.2.1 The Medical Device Directives Process

The process of meeting the requirements of the MDD is a multistep approach, involving the following activities:

- Analyze the device to determine which directive is applicable.
- Identify the applicable essential requirements list.
- Identify any corresponding harmonized standards.
- Confirm that the device meets the essential requirements/harmonized standards and document the evidence.
- Classify the device.
- Decide on the appropriate conformity assessment procedure.
- Identify and choose a Notified Body.
- Obtain conformity certifications for the device.
- Establish a declaration of conformity.
- Apply for the CE mark.

This process does not necessarily occur in a serial manner, but iterations may occur throughout the cycle. Each activity in the process will be examined in detail.

19.2.2 Choosing the Appropriate Directive

Because of the diversity of current national medical device regulations, the commission decided that totally new community legislation covering all medical devices was needed. Software or a medical device containing software may be subject to the requirements of the AIMDD or the MDD.

Three directives are envisaged to cover the entire field of medical devices:

19.2.2.1 AIMDD

This directive applies to a medical device that depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity, which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.

This directive was adopted in June 1990 and implemented in January 1993, and the transition period ended January 1995.

19.2.2.2 MDD

This directive applies to all medical devices and accessories, unless they are covered by the AIMDD or the In Vitro Diagnostic Medical Devices Directive (IVDMDD).

This directive was adopted in June 1993 and implemented in January 1995, and the transition period ended June 1998.

19.2.2.3 IVDMDD

This directive applies to any medical device that is a reagent, reagent product, calibrator, control kit, instrument, equipment, or system intended to be used in vitro for the examination of samples derived from the human body for the purpose of providing information concerning a physiological state of health or disease or congenital abnormality, or to determine the safety and compatibility with potential recipients.

19.2.3 Identifying the Applicable Essential Requirements

The major legal responsibility the directives place on the manufacturer of a medical device requires the device to meet the essential requirements set out in annex I of the directive that applies to them, taking into account the intended purpose of the device. The essential requirements are written in the form of (1) general requirements that always apply and (2) particular requirements, only some of which apply to any particular device.

The general requirements for the essential requirements list take the following form:

- The device must be safe. Any risk must be acceptable in relation to the benefits offered by the device.
- The device must be designed in such a manner that risk is eliminated or minimized.
- The device must perform in accordance with the manufacturer's specification.
- The safety and performance must be maintained throughout the indicated lifetime of the device.
- The safety and performance of the device must not be affected by normal conditions of transport and storage.
- Any side effects must be acceptable in relation to the benefits offered.

The particular requirements for the essential requirements list address the following topics:

- Chemical, physical, and biological properties
- Infection and microbial contamination
- Construction and environmental properties
- Devices with a measuring function
- Protection against radiation
- Requirements for devices connected to or equipped with an energy source
- Protection against electrical risks
- Protection against mechanical and thermal risks
- Protection against the risks posed to the patient by energy supplies or substances
- Information supplied by the manufacturer

The easiest method of assuring that the essential requirements are met is to establish a checklist of the essential requirements from appendix I of the appropriate directive, which then forms the basis of the technical dossier. Table 19.1 is an example of an essential requirements checklist.

The essential requirements checklist includes (1) a statement of the essential requirements, (2) an indication of the applicability of the essential requirements to a particular device, (3) a list of the standards used to address the essential requirements, (4) the activity that addresses the essential requirements, (5) the clause(s) in the standard detailing the applicable test for the particular essential requirement, (6) an indication of whether the device passed/or failed the test, and (7) a statement of the location of the test documentation or certificates.

TABLE 19.1
Example of Essential Requirements Checklist

Essential Requirement	A or N/a	Standards	Activity	Test Clause	Pass/ Fail	Document Location
1. The device must be designed and manufactured in such a way that when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, users, and where applicable, other persons. The risks associated with devices must be reduced to an acceptable level compatible with a high level of protection for health and safety.	A	Internal	Risk analysis Safety review			Design history file Design history file
2. The solutions adopted by the manufacturer for the design and construction of the devices must comply with safety principles and also take into account the generally acknowledged state of the art.	A	Internal	Specification reviews Design reviews Safety review			Design history file Design history file Design history file

19.2.4 Identification of Corresponding Harmonized Standards

A "harmonized" standard is a standard produced under a mandate from the European Commission by one of the European standardization bodies, such as the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC), and that has its reference published in the *Official Journal of the European Communities*.

The essential requirements are worded such that they identify a risk and state that the device should be designed and manufactured so that the risk is avoided or minimized. The technical detail for assuring these requirements is to be found in harmonized standards. Manufacturers must therefore identify the harmonized standards corresponding to the essential requirements that apply to their device.

With regard to choosing such standards, the manufacturer must be aware of the hierarchy of standards that have been developed:

- Horizontal standards: generic standards covering fundamental requirements common to all, or a very wide range of medical devices
- Semi-horizontal standards: group standards that deal with requirements applicable to a group of devices
- Vertical standards: product-specific standards that give requirements to one device or a very small group of devices

Manufacturers must give particular attention to the horizontal standards since, because of their general nature, they apply to almost all devices. As these standards come into use for almost all products, they will become extremely powerful.

Semi-horizontal standards may be particularly important as they have virtually the same weight as horizontal standards for groups of devices, such as orthopedic implants, IVDs, or x-ray equipment.

Vertical standards might well be too narrow to cope with new technological developments when a question of a specific feature of a device arises.

TABLE 19.2
Common Harmonized Standards for Medical Devices

Standard	Areas Covered
EN 60 601 Series	Medical electrical equipment
EN 29000 Series	Quality systems
EN 46000 Series	Quality systems
EN 55011 (CISPR 11)	Electromagnetic compatibility (EMC)/emission
EN 60801 Series	EMC/immunity
EN 540	Clinical investigation of medical devices
EN 980	Symbols on medical equipment
IEC 601-1-2	Medical device emission and immunity
IEC 801-2	Electrostatic discharge
IEC 801-2	Immunity to radiated radio frequency electromagnetic fields
IEC 801-4	Fast transients/burst
IEC 801-5	Voltage surge immunity

Table 19.2 lists some common harmonized standards for medical devices and medical device electromagnetic compatibility standards.

19.2.5 Assurance That the Device Meets the Essential Requirements and Harmonized Standards and Documentation of the Evidence

Once the essential requirements list has been developed and the harmonized standards chosen, the activity necessary to address the essential requirements list must be conducted. Taking the activity on the essential requirements checklist from Table 19.1, the following activity may be conducted to assure that the requirements are met.

19.2.5.1 Essential Requirement 1

This requirement is concerned with the device not compromising the clinical condition or the safety of patient, users, and where applicable, other persons.

The methods used to meet this requirement are the conduction of a hazard analysis and a safety review.

19.2.5.1.1 Hazard Analysis

A hazard analysis is the process, continuous throughout the product development cycle, that examines the possible hazards that could occur due to equipment failure and helps the designer to eliminate the hazard through various control methods. The hazard analysis is conducted on hardware, software, and the total system during the initial specification phase and is updated throughout the development cycle. The hazard analysis is documented on a form similar to that shown in Table 19.3.

The hazard analysis addresses the following issues:

Potential hazard	Identifies possible harm to patient, operator, or system
Generic cause	Identifies general conditions that can lead to the associated potential hazard
Specific cause	Identifies specific instances that can give rise to the associated generic cause
Probability	Classifies the likelihood of the associated potential hazard according to Table 19.4
Severity	Categorizes the associated potential hazard according to Table 19.5
Control mode	Means of reducing the probability and/or severity of the associated potential hazard
Control method	Actual implementation to achieve the associated control mode
Comments	Additional information, references, and so forth

TABLE 19.3
Example of a Hazard Analysis Sheet

Potential Hazard	Generic Cause	Specific Cause	Severity	Control Mode	Control Method	Comments

TABLE 19.4
Hazard Analysis Probability Classification

Classification Indicator	Classification Rating	Classification Meaning
1	Frequent	Likely to occur often
2	Occasional	Will occur several times in the life of the system
3	Reasonably remote	Likely to occur sometime in the life of the system
4	Remote	Unlikely to occur but possible
5	Extremely remote	Probability of occurrence indistinguishable from zero
6	Physically impossible	

TABLE 19.5
Hazard Analysis Severity Classification

Severity Indicator	Severity Rating	Severity Meaning
I	Catastrophic	May cause death or system loss
II	Critical	May cause severe injury, severe occupational illness, or severe system damage
III	Marginal	May cause minor injury, minor occupational illness, or minor system damage
IV	Negligible	Will not result in injury, illness, or system damage

When the hazard analysis is initially completed, the probability and severity refer to the potential hazard prior to its being controlled. As the device is designed to minimize or eliminate the hazard, and control methods are imposed, the probability and severity will be updated.

An organization separate from research and development (R&D), such as quality assurance, reviews the device to assure that it is safe and effective for its intended use. The device, when operated according to specification, must not cause a hazard to the user or the patient. In the conduct of this review, the following may be addressed:

19.2.5.1.2 Safety Review

- Pertinent documentation such as drawings, test reports, and manuals
- A sample of the device
- A checklist specific to the device, which may include the following:
  - Voltages
  - Operating frequencies
  - Leakage currents
  - Dielectric withstand

- Grounding impedance
- Power cord and plug
- Electrical insulation
- Physical stability
- Color coding
- Circuit breakers and fuses
- Alarms, warnings, and indicators
- Mechanical design integrity

The checklist is signed by the reviewing personnel following the analysis.

19.2.5.2 Essential Requirement 2

This requirement is concerned with the device complying with safety principles and the generally acknowledged state of the art. The methods used to meet this requirement are peer reviews and the safety review.

19.2.5.2.1 Peer Review

Peer review of the product specification, design specification, software requirements specification, and the actual design are conducted by qualified individuals not directly involved in the development of the device. The review is attended by individuals from design, reliability, quality assurance, regulatory affairs, marketing, manufacturing, and service. Each review is documented with issues discussed and action items. After the review, the project team assigns individuals to address each action item and a schedule for completion.

19.2.5.2.2 Safety Review

This was discussed under essential requirement 1.

19.2.5.3 Essential Requirement 3

This requirement is concerned with the device achieving the performance intended by the manufacturer. The methods used to meet this requirement are the various specification reviews and the validation of the device to meet these specifications.

19.2.5.3.1 Specification Reviews

This was discussed under essential requirement 2.

19.2.5.3.2 Validation Testing

This activity involves assuring that the design and the product meet the appropriate specifications that were developed at the beginning of the development process. Testing is conducted to address each requirement in the specification and the test plan and test results documented. It is helpful to develop a requirements matrix to assist in this activity.

19.2.5.4 Essential Requirement 4

This requirement is concerned with the device being adversely affected by stresses that can occur during normal conditions of use. The methods used to meet this requirement are environmental testing, environmental stress screening (ESS), and use/misuse evaluation.

19.2.5.4.1 Environmental Testing

Testing is conducted according to Environmental Specifications listed for the product. Table 19.6 lists the environmental testing to be conducted and the corresponding standards and methods employed. Test results are documented.

TABLE 19.6
List of Environmental Testing

Environmental Test	Specification Range	Applicable Standard
Operating temperature	5 to 35 μC	IEC 68-2-14
Storage temperature	−40 to +65 μC	IEC 68-2-1-Ab IEC 68-2-2-Bb
Operating humidity	15%–95% relative humidity (RH) noncondensing	IEC 68-2-30
Operating pressure	500 to 797 mm Hg	IEC 68-2-13
Storage pressure	87 to 797 mm Hg	IEC 68-2-13
Radiated electrical emissions	System: 4 dB margin Subsystem: 15 dB	CISPR 11
Radiated magnetic emissions	System: 4 dB margin Subsystem: 6dB	VDE 871
Line conducted emissions	System: 2 dB margin Subsystem: 2dB	CISPR 11 VDE 871
Electrostatic discharge	Contact: 7 KV Air: 10 KV	EN 60601-2 EN 1000-4-2
Radiated electric field immunity	5 V/m @ 1KHz	EN 60601-2 EN 1000-4-3
Electrical fast transient immunity	Power mains: 2.4 KV Cables >3 m: 1.2 KV	EN 60601-2 EN 1000-4-4
Stability		UL 2601
Transportation		NSTA preshipment
Transportation		NSTA overseas

19.2.5.4.2 ESS

The device is subjected to temperature and vibration stresses beyond that which the device may ordinarily see in order to precipitate failures. The failure may then be designed out of the device before it is produced. ESS is conducted according to a specific protocol that is developed for the particular device. Care must be taken in preparing the protocol to avoid causing failures that would not ordinarily be anticipated. Results of the ESS analysis are documented.

19.2.5.4.3 Use/Misuse Evaluation

Whether through failure to properly read the operation manual or through improper training, medical devices are going to be misused and even abused. There are many stories of product misuse, such as the handheld monitor that was dropped into a toilet bowl, the physician who hammered a 9-volt battery in backward and then reported that the device was not working, or the user that spilled a can of soda on and into a device.

Practically, it is impossible to make a device completely immune to misuse, but it is highly desirable to design around the misuse situations that can be anticipated. These include the following:

- Excess application of cleaning solutions
- Physical abuse
- Spills
- Excess weight applied to certain parts of the device
- Excess torque applied to controls or screws
- Improper voltages, frequencies, or pressures
- Interchangeable electrical or pneumatic connections

Each potential misuse situation should be evaluated for its possible result on the device and a decision made on whether the result can be designed out. Activities similar to these are carried out to complete the remainder of the essential requirements checklist for the device.

19.2.6 Classification of the Device

It is necessary for the manufacturer of a medical device to have some degree of proof that a device complies with the essential requirements before the CE marking can be applied. This is defined as a "conformity assessment procedure." For devices applicable to the AIMDD, there are two alternatives for the conformity assessment procedure. For devices applicable to the IVDMDD, there is a single conformity assessment procedure. For devices applicable to the MDD, there is no conformity assessment procedure that is suitable for all products, as the directive covers all medical devices. Medical devices are therefore divided into four classes, which have specific conformity assessment procedures for each of the four classes.

It is crucial for manufacturers to determine the class into which each of their devices falls. This demands careful study of the classification rules given in annex IX of the directive. As long as the intended purpose, the implementing rules, and the definitions are clearly understood, the classification process is straightforward, and the rules, which are laid out in a logical order, can be worked out in succession from rule 1. If the device is used for more than one intended purpose, then it must be classified according to the one that gives the highest classification.

The rules for determining the appropriate classification of a medical device include the following:

Rule	Type of Device	Class
1–4	Noninvasive devices are in class I except the following:	IIa
	Used for storing body fluids connected to an active medical device in class IIa or higher	
	Modification of body fluids	IIa/IIb
	Some wound dressings	IIa/IIb
5	Devices invasive with respect to body orifices:	I
	Transient use	
	Short-term use	Iia
	Long-term use	IIb
6–8	Surgically invasive devices:	I
	Reusable surgical instruments	
	Transient or short-term use	IIa
	Long-term use	IIb
	Contact with central circulatory system (CCS) or central nervous system (CNS)	III
	Devices that are absorbable or have a biological effect	IIb/III
	Devices that deliver medicines	IIb/III
	Devices applying ionizing radiation	IIb
13	Devices incorporating medicinal products	III
14	Contraceptive devices	IIb/III
15	Chemicals used for cleaning or disinfecting:	IIa
	Medical devices	
	Contact lenses	IIb
16	Devices specifically intended for recording x-ray images	IIa
17	Devices made from animal tissues	III
18	Blood bags	IIb

In the cases of active devices, the rules are based mainly on the purpose of the device, that is, diagnosis or therapy, and the corresponding possibility of absorption of energy by the patient.

Rule	Type of Device	Class
9	Therapeutic devices administering or exchanging energy	IIa
	If operating in a potentially hazardous way	IIb
10	Diagnostic devices:	IIa
	Supplying energy other than illumination	
	Imaging radiopharmaceuticals in vivo	IIa
	Diagnosing/monitoring vital functions	IIa
	Monitoring vital functions in critical care conditions	IIb
	Emitting ionizing radiation	IIb
11	Active devices administering/removing medicines/body substances	IIa
	If operating in a potentially hazardous way	IIb
12	All other active devices	I

In order to use the classification system correctly, manufacturers must have a good understanding of the implementing rules and definitions.

The key implementing rules include the following:

- Application of the classification rules is governed by the intended purpose of the device.
- If the device is intended to be used in combination with another device, the classification rules are applied separately to each device.
- Accessories are classified in their own right, separately from the device with which they are used.
- Software, which drives a device or influences the use of a device, falls automatically in the same class as the device itself.

19.2.7 Decision on the Appropriate Conformity Assessment Procedure

19.2.7.1 Medical Devices Directive

There are six conformity assessment annexes to the Medical Devices Directive. Their use for the different classes of devices is specified in article 11 of the directive.

19.2.7.1.1 Annex II

This annex describes the system of full quality assurance covering both the design and manufacture of devices.

19.2.7.1.2 Annex III

This annex describes the type of examination procedure according to which the manufacturer submits full technical documentation of the product, together with a representative sample of the device to a Notified Body.

19.2.7.1.3 Annex IV

This annex describes the examination by the Notified Body of every individual product, or one or more samples from every production batch, and the testing that may be necessary to show the conformity of the products with the approved/documented design.

19.2.7.1.4 Annex V

This annex describes a production quality system that is to be verified by a Notified Body as assuring that devices are made in accordance with an approved type, or in accordance with technical documentation describing the device.

19.2.7.1.5 Annex VI

This annex describes a quality system covering final inspection and testing of products to ensure that devices are made in accordance with an approved type, or in accordance with technical documentation.

19.2.7.1.6 Annex VII

This annex describes the technical documentation that the manufacturer must compile in order to support a declaration of conformity for a medical device, where there is no participation of a Notified Body in the process.

The class to which the medical device is assigned has an influence on the type of conformity assessment procedure chosen.

19.2.7.1.7 Class I

Compliance with the essential requirements must be shown in technical documentation compiled according to annex VII of the directive.

19.2.7.1.8 Class IIa

The design of the device and it compliance with the essential requirements must be established in technical documentation described in annex VII. However, for this class, agreement of production units with the technical documentation must be assured by a Notified Body according to one of the following alternatives:

- Sample testing — Annex IV
- An audited production quality system — Annex V
- An audited product quality system — Annex VI

19.2.7.1.9 Class IIb

The design and manufacturing procedures must be approved by a Notified Body as satisfying annex II, or the design must be shown to conform to the essential requirements by a type examination (annex III) carried out by a Notified Body.

19.2.7.1.10 Class III

The procedures for this class are similar to class IIb, but significant differences are that when the quality system route is used, a design dossier for each type of device must be examined by the Notified Body. Clinical data relating to safety and performance must be included in the design dossier or the documentation presented for the type of examination.

19.2.7.2 Active Implantable Medical Devices Directive

For devices following the AIMDD, annexes II through V cover the various conformity assessment procedures available. There are two alternative procedures:

19.2.7.2.1 Alternative 1

A manufacturer must have in place a full quality assurance system for design and production and must submit a design dossier on each type of device to the Notified Body for review.

19.2.7.2.2 Alternative 2

A manufacturer submits an example of each type of his/her device to a Notified Body, satisfactory production must be assured by either the quality system at the manufacturing site or by compliance with EN 29002 + EN 46002 and must be audited by a Notified Body, or samples of the product must be tested by a Notified Body.

19.2.7.3 In Vitro Diagnostic Medical Devices Directive

For devices adhering to the IVDMDD, the conformity assessment procedure is a manufacturer's declaration. In vitro devices for self-testing must additionally have a design examination by a Notified Body or be designed and manufactured in accordance with a quality system.

In choosing a conformity assessment procedure, it is important to remember that (1) it is essential to determine the classification of a device before deciding on a conformity assessment procedure; (2) it may be more efficient to operate one conformity assessment procedure throughout a manufacturing plant, even though this procedure may be more rigorous than strictly necessary for some products; and (3) tests and assessments carried out under current national regulations can contribute toward the assessment of conformity with the requirements of the directives.

19.2.8 Type Testing

A manufacturer of class IIb or class III medical devices can choose to demonstrate that his/her device meets the essential requirements by submitting to a Notified Body for a type examination as described in annex III of the directive. The manufacturer is required to submit technical documentation on his/her device together with an example of the device. The Notified Body will then carry out such tests as it considers necessary to satisfy itself, before issuing the EC Type Examination Certificate.

Type testing of many kinds of medical devices, particularly electromedical equipment, is required under some current national regulations. Manufacturers who are familiar with this process and who have established relations with test houses that are or will be appointed as Notified Bodies are likely to find this a more attractive procedure than the design control procedures of EN29001/EN46001. Existing products that have already been type tested under current national procedures are likely to meet most of the essential requirements and may require little or no further testing. Testing by one of the nationally recognized test houses may also be a means to gain entitlement to national or proprietary marks, which can be important in terms of market acceptance.

A major issue in type examination is the handling of design and manufacturing changes. Annex III states that the manufacturer must inform the Notified Body of any significant change made to an approved product and that the Notified Body must give further approval if the change could affect conformity with the essential requirements. The meaning of *significant change* must be negotiated with the Notified Body, but clearly, for certain products or for manufacturers with a large number of products, the notification and checking of changes could impose a serious burden.

When a change could have an effect on the compliance with the essential requirements, the manufacturer should make his/her own assessment, including tests, to determine that the device still complies and submit updated drawings and documentation, together with the test results. The Notified Body must be informed of all changes made as a result of an adverse incident.

When the assessment is that the changes are not liable to have an effect, they should be submitted to the Notified Body "for information only." The manufacturer must, in such cases, keep records of the change and of the rationale for the conclusion that the change could not have an effect.

19.2.9 Identification and Choice of a Notified Body

Identifying and choosing a Notified Body is one of the most critical issues facing a manufacturer. A long-term and close relationship should be developed, and time and care spent in making a careful choice of a Notified Body should be viewed as an investment in the future of the company.

Notified bodies must satisfy the criteria given in annex XI of the Medical Device Directive, namely,

- Independence from the design, manufacture, or supply of the devices in question
- Integrity

- Competence
- Staff who are trained, experienced, and able to report
- Impartiality of the staff
- Possession of liability insurance
- Professional secrecy

In addition, the bodies must satisfy the criteria fixed by the relevant harmonized standards. The relevant harmonized standards include those of the EN 45000 series dealing with the accreditation and operation of certification bodies.

The tasks to be carried out by Notified Bodies include the following:

- Audit manufacturers; quality systems for compliance with annexes II, V, and VI.
- Examine any modifications to an approved quality system.
- Carry out periodic surveillance of approved quality systems.
- Examine design dossiers and issue EC Design Examination Certificates.
- Examine modifications to an approved design.
- Carry out type examinations and issue EC Type Examination Certificates.
- Examine modifications to an approved type.
- Carry out EC verification.
- Take measures to prevent rejected batches from reaching the market.
- Agree with the manufacturer time limits for the conformity assessment procedures.
- Take into account the results of tests or verifications already carried out.
- Communicate to other Notified Bodies (on request) all relevant information about approvals of quality systems issued, refused, and withdrawn.
- Communicate to other Notified Bodies (on request) all relevant information about EC Type Approval Certificates issued, refused, and withdrawn.

Notified bodies must be located within the EC in order that effective control may be applied by the competent authorities that appointed them, but certain operations may be carried out on behalf of Notified Bodies by subcontractors who may be based outside the EC. Competent authorities will generally notify bodies on their own territory, but they may notify bodies based in another member state provided that they have already been notified by their parent Competent Authority.

There are several factors to be taken into account by a manufacturer in choosing a Notified Body, including the following:

- Experience with medical devices
- Range of medical devices for which the Notified Body has skills
- Possession of specific skills, for example, EMC or software
- Links with subcontractors and subcontractor skills
- Conformity assessment procedures for which the body is notified
- Plans for handling issues, such as clinical evaluation
- Attitude to existing certifications
- Queue times/processing times
- Costs
- Location and working languages

Experience with medical devices is limited to a small number of test houses, and their experience is largely confined to electromedical equipment. Manufacturers should probe carefully the competence of the certification body to assess their device. Actual experience with a product of a similar nature would be reassuring. The certification body should be pressed to

demonstrate sufficient understanding of the requirements, particularly where special processes are involved (e.g., sterilization), and/or previous experience.

Certain devices demand specific skills that may not be found in every Notified Body. Clearly, the Notified Body must have, or be able to obtain, the skills required for the manufacturer's devices.

Many Notified Bodies will supplement their in-house skills by the use of specialist subcontractors. This is perfectly acceptable as long as all the rules of subcontracting are followed. Manufacturers should verify for themselves the reputation of the subcontractor and the degree of supervision applied by the Notified Body.

The main choice open to manufacturers is full quality system certification or type examination combined with one of the less rigorous quality system certifications. Some Notified Bodies have a tradition of either product testing or systems evaluation, and it therefore makes sense to select a Notified Body with experience in the route chosen.

A clinical evaluation is required for some medical devices, especially class III devices and implants. Although this will be a key aspect of demonstrating conformity, it will be important for manufacturers to know how the Notified Body intends to perform this function.

In preparing the Medical Device Directives, the need to avoid reinventing the wheel has been recognized. In order to maximize this need, companies whose products have already been certified by test houses that are likely to become Notified Bodies may wish to make use of the organizations with whom they have previously worked. It will be important to verify with the Notified Body the extent to which the testing previously performed is sufficient to meet the essential requirements.

At the time of this writing, most Notified Bodies seem to be able to offer fairly short lead times. The time for actually carrying out the examination or audit should be questioned. It must be remembered that manufacturers will have to pay Notified Bodies for carrying out the conformity assessment procedures. There will certainly be competition, and this may offer some control over costs. Although it will always be a factor, the choice of a Notified Body should not be governed by cost alone, bearing in mind the importance of the exercise.

For obvious reasons of expense, culture, convenience, and language, there will be a tendency for European manufacturers to use a Notified Body situated in their own country. Nevertheless, this should not be the principal reason for selection, and account should be taken of the other criteria discussed here. For manufacturers outside the EC, the geographical location is less important. Of greater significance to them, particularly U.S. companies, is the existence of overseas subsidiaries or subcontractors of some of the Notified Bodies. Manufacturers should understand that the Notified Body must be a legal entity established within the member state that has notified it. This does not prevent the Notified Body subcontracting quite significant tasks to a subsidiary.

Article 11.12 states that the correspondence relating to the conformity assessment procedures must be in the language of the member state in which the procedures are carried out and/or in another community language acceptable to the Notified Body. Language may thus be another factor affecting the choice of Notified Body, although most of the major certification bodies will accept English and other languages.

The most significant factor of all is likely to be existing good relations with a particular body. Notified Bodies will be drawn from existing test and certification bodies, and many manufacturers already use such bodies, either as part of a national approval procedure or as part of their own policy for ensuring the satisfactory quality of their products and processes.

Another consideration that could become significant is that of variations in the national laws implementing the directives. Notified Bodies will have to apply the law of the country in which they are situated, and some differences in operation could be introduced by this means.

19.2.10 Establishing a Declaration of Conformity

Of all documents prepared for the Medical Device Directives, the most important may be the declaration of conformity. Every device, other than a custom-made or clinical investigation device, must be covered by a declaration of conformity.

The general requirement is that the manufacturer shall draw up a written declaration that the products concerned meet the provisions of the directive that apply to them. The declaration must cover a given number of the products manufactured. A strictly literal interpretation of this wording would suggest that the preparation of a declaration of conformity is not a one-and-for-all event with an indefinite coverage but, rather, a formal statement that products that have been manufactured and verified in accordance with the particular conformity assessment procedure chosen by the manufacturer do meet the requirements of the directive. Such an interpretation would impose severe burdens on manufacturers, and the commission is understood to be moving to a position where a declaration of conformity can be prepared in respect of future production of a model of a device for which the conformity assessment procedures have been carried out. The CE marking of individual devices after manufacture can then be regarded as a short-form expression of the declaration of conformity in respect to that individual device. This position is likely to form part of future commission guidance.

Even so, the declaration remains a very formal statement from the manufacturer and, accordingly, must be drawn up with care. The declaration must include the serial numbers or batch numbers of the products it covers, and manufacturers should give careful thought to the appropriate coverage of a declaration. In the extreme, it may be that a separate declaration should be prepared individually for each product or batch.

A practical approach is probably to draw up one basic declaration that is stated to apply to the products whose serial (batch) numbers are listed in an appendix. The appendix can then be added to at sensible intervals. A suggested format is shown in Figure 19.1.

19.2.11 Application of the CE Mark

The CE marking (Figure 19.2) is the symbol used to indicate that a particular product complies with the relevant essential requirements of the appropriate directive and, as such, that the product has achieved a satisfactory level of safety and thus may circulate freely throughout the community.

It is important to note that it is the manufacturer or his/her authorized representative who applies the CE marking to the product and not the Notified Body. The responsibility for ensuring that each and every product conforms to the requirements of the directive is that of the manufacturer, and the affixing of the CE marking constitutes the manufacturer's statement that an individual device conforms.

Name (print or type): _____

Title: _____

Signature: _____

Date: _____

FIGURE 19.1 Sample declaration of conformity.

FIGURE 19.2 Example of CE mark.

DECLARATION OF CONFORMITY

We: *Company Name*
Company Address

Declare that the product(s) listed below:

Product(s) to be declared

hereby conform(s) to the European Council Directive 93/42/EEC, Medical Device Directive, Annex II, Article 3. This declaration is based on the Certification of the Full Quality Assurance System by *name of Notified Body*, Notified Body # XXXX.

FIGURE 19.3 Sample declaration of conformance.

The CE marking should appear on the device itself, if practicable, on the instructions for use, and on the shipping packaging. It should be accompanied by the identification number of the Notified Body that has been involved in the verification of the production of the device. It is prohibited to add other marks that could confuse or obscure the meaning of the CE marking.

The XXXX noted in Figure 19.3 is the identification number of the Notified Body.

19.2.12 Conclusion

Compliance with the EC directives forced major changes for medical device manufacturers. Such changes relate to the requirements to be met in view of the design and manufacture of medical devices as well as to the procedures to be followed by manufacturers prior to and after placing medical devices on the European market. Manufacturers who wish to market medical devices in the EC are therefore faced with a quite far-reaching and rather complex decision-making process.

19.3 SOFTWARE STANDARDS AND REGULATIONS

There are a myriad of software standards to assist the developer in designing and documenting his/her program. IEEE standards cover documentation through all phases of design. Military standards describe how software is to be designed and developed for military use. There are also standards on software quality and reliability to assist developers in preparing a quality program. The international community has produced standards, primarily dealing with software safety. In each case, the standard is a voluntary document that has been developed to provide guidelines for designing, developing, testing, and documenting a software program.

In the United States, the Food and Drug Administration (FDA) is responsible for assuring that the device utilizing software or the software as a device is safe and effective for its intended use. The FDA has produced several drafts of reviewer guidelines, auditor guidelines, software policy, and Good Manufacturing Practices (GMP) regulations addressing both device and process software. In addition, guidelines for FDA reviewers have been prepared as well as training programs for inspectors and reviewers. The GMP regulation also addresses software as part of the design phase.

The United States is ahead of other countries in establishing guidelines for medical software development. There is, however, movement within several international organizations to develop regulations and guidelines for software and software-controlled devices. For example, ISO 9000-3 specifically addresses software development in addition to what is contained in ISO 9001. The Canadian Standards Association (CSA) addresses software issues in four standards covering new and previously developed software in critical and noncritical applications. IEC 62304 is a document addressing the software development process.

19.4 REST-OF-WORLD STANDARDS

No country regulates medical devices as consistently and thoroughly as the United States. However, there is a trend toward regulation in other industrialized countries, especially in Europe. France requires registration and evaluation of medical devices for public hospitals. Germany requires the registration of all medical devices linked to approval by defined testing organizations. England's Department of Health and Social Security is active in evaluating selected devices. And Italy requires registration of all medical devices marketed in that country.

In Europe, an important international organization working in the area of devices is the EC. The EC has directives dealing with medical equipment. For example, under EC directives, all governments are required to develop standards for x-ray machines and x-ray therapy. Another EC directive, issued by the International Electrotechnical Committee (IEC), requires member states to set standards for electrical safety. An EC working group on biomedical engineering focuses on the safety of medical equipment. The World Health Organization, especially the European Office in Copenhagen, has become increasingly involved in medical devices, especially promoting the idea of international exchange of information. International cooperation and communication could make much more information on medical equipment available and save evaluation resources of all countries.

19.4.1 The International Notion of Standards

The British Standards Institute defines a standard as follows:

> A technical specification or other document available to the public, drawn up with the cooperation and consensus or general approval of all interests affected by it, based on the consolidated results of science, technology, and experience, aimed at the promotion of optimum community benefits and approved by a body on the national, regional, or international level.

While this definition goes some way toward saying what a standard is, it says nothing about the subject matter or purpose, apart from stating that the objectives of the standard must, in some way, be tied to community benefits.

Standards, however, have a definite subject matter. They include the following:

- Standardization of particular processes
- Provision of a consistent and complete definition of a commodity or process
- Recording of good practice regarding the development process associated with the production of commodities
- Encoding of good practice for the specification, design, manufacture, testing, maintenance, and operation of commodities

One of the primary requirements of a standard is that it be produced in such a way that conformance to it can be unambiguously determined. A standard is devalued if conformance cannot be easily determined or if the standard is so loosely worded that it becomes a matter of debate and conjecture as to whether the standard has been complied with.

Standards also exist in various types:

- *De facto and de jure standards.* These are usually associated with the prevailing commercial interests in the marketplace. These de facto standards are often eventually subject to the standardization process.
- *Reference models.* These provide a framework within which standards can be formulated.
- *Product versus process standards.* Some standards relate to specific products, while others relate to the process used to produce products.

- *Codes of practice, guidelines, and specifications.* These terms relate to the manner in which a standard may be enforced. Codes of practice and guidelines reflect ways of working that are deemed to be *good* or *desirable* but for which conformance is difficult to determine. Specifications are far more precise, and conformance can be determined by analysis or test.
- *Prospective and retrospective standards.* It is clearly undesirable to develop a standard before the subject matter is well understood scientifically, technically, and through practice. However, it may be desirable to develop a standard alongside the evolving technology.

19.4.2 The International Regulatory Scene

The production and adoption of software standards is very much the responsibility of international and national standards organizations, and in the case of the European context, bodies set up to represent a number of national organizations. Progressively, it is becoming the case that standards are developed by the international bodies and then adopted by the national bodies. Some of the international bodies include the following:

- *BSI.* The British Standards Institute is the United Kingdom's national standards-making organization. In performing its duties, it collaborates with industry, government agencies, other standard bodies, professional organizations, and so forth.
- *CEN.* The Comite Europeen de Normalisation (European Committee for Standardization) is composed of members drawn from the European Union (EU) and the EFTA. The role of CEN is to produce standards for use within Europe and effectively covers the area addressed by the International Standards Organization (ISO).
- *CENELEC.* The Comite Europeen de Normalisation Electronique (European Committee for Electrotechnical Standardization) is made up of representatives from the national electrotechnical committees, the majority of whom are represented on the IEC. Its responsibilities are for electrical and electronic standards within Europe, and it has close links with the activities of the IEC.
- *CISPR.* The International Special Committee on Radio Interference is a committee under the auspices of the IEC and run through a Plenary Assembly consisting of delegates from all the member bodies, including the United States. The committee is headquartered in Geneva, Switzerland, and is composed of seven subcommittees, including the following:
  - Radio Interference Measurement and Statistical Methods
  - Interference from Industrial, Scientific, and Medical Radio Frequency Apparatus
  - Interference from Overhead Power Lines, High Voltage Equipment, and Electric Traction Systems
  - Interference Related to Motor Vehicles and Internal Combustion Engines
  - Interference Characteristics of Radio Receivers
  - Interference from Motor, Household Appliances, Lighting Apparatus, and the Like
  - Interference from Information Technology Equipment
- *CSA.* The Canadian Standards Association is a membership association that brings people and ideas together to develop services that meet the needs of businesses, industry, governments, and consumers. Among the many services available are standards development, testing and application of the CSA mark to certified products, testing to international standards, worldwide inspection, and related services.
- *DIN.* The Deutsches Institut für Normung (German Standardization Institute) is the committee that sets German standards.
- *DOH.* The Department of Health has the same responsibility in England that the FDA has in the United States. DOH sets forth standards for medical devices and has established a GMP for medical equipment, similar to that of the FDA. DOH is headquartered in London.

DOH currently has reciprocity with the FDA, meaning the FDA will accept DOH inspection data as their own and DOH will accept FDA inspection data. This is particularly applicable for companies with facilities in both England and the United States.

- *IEC*. The International Electrotechnical Commission was established in 1906 with the responsibility for developing international standards within the electrical and electronics field. By agreement with the International Standards Organization, the IEC has sole responsibility for these standards.
- *IEE*. The Institution of Electrical Engineers is the main UK professional body responsible for electrical and electronic engineering. It is responsible for the production of a wide range of standards in the electrical engineering field and is progressively widening its interests to include software engineering.
- *ISO*. The International Standards Organization was established in 1947, and its members are drawn from the national standards bodies of its members. ISO is responsible for standardization in general but with the exception of electrical and electronic standards, which are the responsibility of the IEC.
- *JSA*. The Japanese Standards Association was established as a public institution for the promotion of industrial standardization on December 6, 1945, under government authorization. JSA has no true performance standards but tends to follow IEC 601-1. JSA does have a complicated approval process that can be very lengthy (up to 9 months). This process can delay distribution of products in Japan. JSA activities include the following:
  - Standards and document publishing
  - Seminars and consulting services
  - Research on standardization
  - National sales agent for foreign national standard bodies
- *Other Japanese Standards Organizations*. The unified national system of industrial standardization began to function by the setup of the Japanese Engineering Standards Committee (JESC) in 1921. This group undertook the establishment of national standards. In 1949, the Industrial Standardization Law was promulgated, and the Japanese Industrial Standards Committee (JISC) was established under the law as an advisory organization of competent ministers in charge of the elaboration of Japanese Industrial Standards (JIS) and the designation of the JIS mark to products.

19.4.3 The TickIT Program

The TickIT project came from two studies commissioned by the Department of Trade and Industry (DTI), which showed that the cost of poor quality in software in the United Kingdom was very considerable and that quality system certification was desired by the market. The studies undertook extensive research into the respective subjects and included a broad consultative process with users, suppliers, in-house developers, and purchasers, with a primary task being to identify options for harmonization. The reports made a number of significant recommendations, including the following:

- All quality management system (QMS) standards in common use were generically very similar.
- The best harmonization route was through ISO 9001.
- Action was required to improve market confidence in third party certifications of QMSs.
- There was an urgent need to establish an accredited certification body or bodies for the software sector.

These principal recommendations were accepted by the DTI, and further work was commissioned with the British Computer Society (BCS) to set up an acceptable means to gain accredited certification of QMSs by auditors with necessary expertise. Draft guidance material for an

acceptable certification scheme was developed. The onward development from this draft material has become known as the TickIT project.

TickIT is principally a certification scheme, but this is not its primary purpose. The main objectives are to stimulate developers to think about what quality really is and how it may be achieved. Unless certification is purely a by-product of these more fundamental aims, much of the effort will be wasted. To stimulate thinking, TickIT includes some quality themes that give direction to the setting up of a QMS and the context of certification.

Generally, TickIT certification applies for information technology (IT) systems supply where software development forms a significant or critical part. The main focus of TickIT is software development because this is the component that gives an information system its power and flexibility. It is also the source of many of the problems.

19.4.4 The Software Quality System Registration Program

The Software Quality System Registration Committee was established in 1992. The Committee's charter was to determine whether a program should be created in the United States for ISO 9001 registration of software design, production, and supply. A comparable program, TickIT, had been operational in the United Kingdom for over 1 year and was gaining European acceptance. To ensure mutual recognition and to leverage the experience of the worldwide software industry, the Software Quality System Registration (SQSR) program preserves ISO 9001 as the sole source for requirements and ISO 9000-3 as a source of official guidance for software registrants.

The SQSR program is designed for ISO 9001 registration of suppliers who design and develop software as a significant or crucial element in the products they offer. The SQSR program addresses the unique requirements of software engineering and provides a credible technical basis to allow the Registrar Accreditation Board (RAB) to extend its current programs for accrediting ISO 9000 registrars, certifying auditors, and accrediting specific courses and course providers.

The program is intended to ensure that ISO registration is an effective, enduring indicator of a software supplier's capability. The effectiveness of the SQSR program is based on three factors: mutual recognition, guidance, and an administrative infrastructure tailored to the U.S. marketplace.

19.4.5 The ISO Guidance Documents for ISO 9001 and 9002

ISO Technical Committee 210 has recently developed two guidelines relating ISO 9001 and 9002 to medical devices. The 1994 version of ISO 9001 and 9002 are intended to be general standards defining quality system requirements. ISO 13485 provides particular requirements for suppliers of medical devices that are more specific than the general requirements of ISO 9001. ISO 13488 provides particular requirements for suppliers of medical devices that are more specific than the general requirements of ISO 9002.

In conjunction with ISO 9001 and 9002, these international standards define requirements for quality systems relating to the design, development, production, installation, and servicing of medical devices. They embrace all the principles of the GMPs used in the production of medical devices.

They specify the quality system requirements for the production and, where relevant, installation of medical devices. They are applicable when there is a need to assess a medical device supplier's quality system or when a regulatory requirement specifies that this standard shall be used for such assessment. As part of an assessment by a third party for the purpose of regulatory requirements, the supplier may be required to provide access to confidential data in order to demonstrate compliance with one of these standards. The supplier may be required to exhibit these data but is not obliged by the standard to provide copies for retention.

Particular requirements in a number of clauses of these standards are covered in detail in other international standards. Suppliers should review the requirements and consider using the relevant international standards in these areas.

19.4.6 ISO 14000 Series

ISO formed Technical Committee 207 in 1993 to develop standards in the field of environmental management tools and systems. The ISO 14000 series encompasses seven areas:

- Management systems
- Audits
- Labeling
- Environmental performance evaluation
- Life cycle assessment
- Terms and definitions
- Environmental aspects in product standards

They are not product standards, nor do they specify performance or pollutant/effluent levels. They specifically exclude test methods for pollutants and do not set limit values regarding pollutants or effluents.

The 14000 standards promote the broad interests of the public and users, emphasize cost-effectiveness, and are more easily accepted and implemented. The goal is to improve environmental protection and quality of life.

ISO 14000 provides for the basic tenets of an environmental management system (EMS). An EMS is the management system that addresses the environmental impact of a company's processes and products on the environment. The EMS provides a formalized structure for ensuring that environmental concerns are addressed and met and works to both control a company's significant environmental effects and achieve regulatory compliance.

The certification process for ISO 14000 has six steps:

- Quality documentation review
- Initial visit, preassessment, or checklist
- On-site audit
- Follow-up audits to document corrective action
- Periodic audits to document compliance
- Renewal audit every 3–5 years

Currently, there is limited correlation between ISO 14000 and ISO 9000, but the requirements of the two series may become more harmonized in the future. Under certain conditions, the ISO 14000 audit and the ISO 9000 audit can be combined into one. It has been estimated that the cost of complying to ISO 14000 would be comparable to that for certification to ISO 9000. The registration process itself could take up to 18 months to complete.

In the United States, ANSI has established a national program to accredit ISO 14000 registrars, auditor certifiers, and training providers. The ISO 14000 registrars are likely to come from the registrars currently performing certifications in ISO 9000.

The creation of a universal single set of EMS standards will help companies and organizations to better manage their environmental affairs and show a commitment to environmental protection. It should also help them avoid multiple registrations, inspections, permits, and certifications of products exchanged among countries. In addition, it should concentrate worldwide attention on environmental management. The World Bank and other financial institutions may qualify their loans to less developed countries and begin to use the 14000 standards as an indicator of commitment to environmental protection.

In the United States, implementation of ISO 14000 could become a condition of business loans to companies that are not even involved in international trade. Insurance companies may lower premiums for those who have implemented the standard. It may become a condition of some supplier

transactions, especially in Europe and with the U.S. government. Evidence of compliance could become a factor in regulatory relief programs, the exercise of prosecutorial and sentencing discretion, consent decrees and other legal instruments, and multilateral trade agreements. U.S. government agencies considering the ISO 14000 standards include the following:

- The Environmental Protection Agency
- The Department of Defense
- The Department of Energy
- The Food and Drug Administration
- The National Institute of Standards and Technology
- The Office of the U.S. Trade Representative
- The Office of Science and Technology Policy

19.4.7 Medical Informatics

The real world is perceived as a complex system characterized by the existence of various parallel autonomous processes evolving in a number of separate locations, loosely coupled, cooperating by the interchange of mutually understandable messages. Due to the fact that medical specialties, functional areas, and institutions create, use, and rely on interchanged information, they should share a common basic understanding in order to cooperate in accordance with a logical process constrained under an administrative organization, medical heuristics, and an approach to care.

A health care framework is a logical mapping between the real world, in particular, the health care environment, and its health care information systems architecture. This framework, representing the main health care subsystems, their connections, rules, and so forth is the basis for an evolutionary development of heterogeneous computer-supported health care information and communications systems. A key feature of the framework is its reliance on the use of abstractions. In this way, the framework, at its most abstract level, reflects the fundamental and essential features of health care processes and information and can be seen as applicable to all health care entities. It defines the general information structure and enables the exchangeability of the information.

The European health care framework will maintain and build upon the diversity of national health care systems in the European countries. A harmonized description/structure of planning documentation will be provided to ensure comparisons between European countries.

The main rationale for a standardized health care information framework is as follows:

- To act as a contract between the users and procurers on the one hand and the developers and providers of information systems on the other
- To ensure that all applications and databases are developed to support the health care organization as a whole as opposed to just a single organization or department
- To obtain economies of scale, originating from enhanced portability, as health care information systems are expensive to develop and to maintain, and tend to be installed on an international basis
- To define a common basic understanding that allows all health care information systems to interchange data

EXERCISES

1. Compare the EU and the FDA definitions of a medical device. What is similar? What differs?
2. Perform a web search with ISO 9000 as the search term. You likely will turn up several companies that offer ISO 9000 and related services. What are the companies really offering (guidance/advice/consulting)? Justify your answer.

3. You have developed a portable device that monitors the EEG of patients prone to grand mal seizures. If one is predicted, your device automatically injects a drug to stop the impending seizure. How would this device be classified in the United States? In the European Union?
4. Same as question 3, but the device only warns the patient.
5. Visit the website http://www.ghtf.org/. Briefly report on the purposes of the four study groups listed. Why do you think such a group is needed?
6. You manufacture a device currently accepted by the FDA. Why would you wish to get CE certification?

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20 Intellectual Property
Patents, Copyrights, Trade Secrets, and Licensing

> Ultimately property rights and personal rights are the same thing.
>
> **Calvin Coolidge**

> The march of invention has clothed mankind with powers of which a century ago the boldest imagination could not have dreamt.
>
> **Henry George**

Intellectual property (IP) is a generic term used to describe the products of the human intellect that have economic value. IP is "property" because a body of laws has been created over the last 200 years that gives owners of such works legal rights similar in some respects to those given to owners of real estate or tangible personal property. IP may be owned, bought, leased (licensed), and sold the same *way* as other types of property.

There are four separate bodies of law that may be used to protect IP. These are patent law, copyright law, trademark law, and trade secret law. Each of these bodies of law may be used to protect different aspects of IP, although there is a great deal of overlap among them.

20.1 PATENTS

A patent is an official document, issued by the U.S. government or another government, which describes an invention and confers on the inventors a monopoly over the disposition of the invention. The monopoly allows the patent owner to go to court to stop others from making, selling, using, *or importing* the invention without the patent owner's permission. This amounts to a "fence around the property," the property being the patent itself.

Generally, an invention is any device or process that is based on an original idea conceived by one or more inventors and is useful in getting something done or solving a problem. An invention may also be a nonfunctional unique design or a plant. But when the word "invention" is used out in the technical world, it frequently implies a "utility patent," which means a composition, device, or process. In order for an invention to be patentable, it must meet three criteria: novelty, nonobviousness, and usefulness. Many inventions, while extremely clever, do not qualify for patents, primarily because they are not considered to be sufficiently innovative in light of previous developments. The fact that an invention is not patentable does not necessarily mean that it has no value for its owner.

There are three types of patents that can be created: utility, design, and plant patents. Table 20.1 compares the three types of patents and the monopoly each type grants to the author.

20.1.1 What Qualifies as a Patent?

An invention must meet several basic legal tests in order to qualify as a patent. These include the following:

TABLE 20.1
Patent Monopolies

Type of Patent	Legal Test	Length of Monopoly (Years from Application Date)
Utility	Useful/nonobvious/improvement/novel design of process/machine/matter	20
Design	New, nonobvious design or appearance ("look"); a single claim is allowed	14
Plant	New or discovered and asexually reproduced plant or variety, nontuberous, may include algae and fungi, not bacteria	20

- Patentable subject matter
- Usefulness
- Novelty
- Nonobviousness
- An improvement over an existing invention
- A design
- A plant

We will concentrate primarily on the utility patent here. The plant patent would be of concern for a design text in agricultural engineering or bioengineering; the design patent is more of concern for those working in industrial design. A design patent only protects the ornamental features of a product. An example of a plant patent would be for a new variety of rose. A design patent example would be a uniquely shaped bumper on a new car.

20.1.1.1 Patentable Subject Matter

The most fundamental qualification for a patent is that the invention consists of patentable subject matter. The patent laws define patentable subject matter as inventions that are one of the following:

- A process or method
- A machine or apparatus
- An article of manufacture
- A composition of matter
- A new and useful improvement of an invention in any of these classes

Computer software is included in the previous category and has been since the early 1990s. The topic of patentable subject matter becomes very interesting when dealing with biological materials, for example, DNA, RNA, and so forth.

20.1.1.2 Usefulness

Almost always, an invention must be useful in some way to qualify for a patent. Fortunately, this is almost never a problem, since virtually everything can be used for something.

20.1.1.3 Novelty

As a general rule, no invention will receive a patent unless it is different in some important way from previous inventions and developments in the field, whether patented or not. To use legal jargon, the invention must be novel over the prior art. The basic test for this criterion is as follows: has anyone (including the inventor) reported this invention before (in written or oral form) in a manner that will

allow someone else to duplicate the invention (enabling disclosure)? Thus, it is recommended that one is to be careful about conference proceedings, poster presentations, publications, and so forth in advance of patent filing. Once disclosed, you have 1 year to file a patent (in the United States). In the rest of the world, countries depend on "absolute novelty"; that is, the invention has not been disclosed prior to the patent application. On March 16, 2013, U.S. patent law was updated to correspond to the international standard of "first to file"; that is, if two inventors have the same invention, then the first one to file an application is eligible for the patent, irrespective of who invented the invention first. As of 2014, you must also be "first to file."

20.1.1.4 Nonobviousness

In addition to being novel, an invention must have a quality that is referred to as "nonobviousness." This means that the invention would have been surprising or unexpected to someone who is familiar with the field of the invention ("one skilled in the art"). In deciding whether an invention is nonobvious, the United States Patent and Trademark Office (USPTO) may consider all previous developments (prior art) that existed when the patent application for the invention was first submitted. Obviousness is a quality that is difficult to define, but supposedly, patent examiners know it when they see it, and it is often the basis for vigorous debate between patent lawyers and patent examiners.

As a general rule, an invention is considered nonobvious when it does one of the following:

- Solves a problem that people in the field have been trying to solve for some time
- Does something significantly quicker than was previously possible
- Performs a function that could not be performed before

20.1.1.5 Improvement of an Existing Invention

Earlier, we noted that to qualify for a patent, an invention must fit into at least one of the statutory classes of matter entitled to a patent—a process, a machine, a manufacture, a composition of matter, or an improvement of any of these. As a practical matter, this statutory classification is not very important since even an improvement on an invention in any one of the statutory classes will also qualify as an actual invention in that class. In other words, an invention will be considered as patentable subject matter as long as it fits within at least one of the other four statutory classes—whether or not it is viewed as an improvement or an original invention. However, the improvement must still meet the three tests for patentability: novelty, nonobviousness, and usefulness.

20.1.1.6 A Design Patent

Design patents are granted to new, original, and ornamental designs that are a part of articles of manufacture. Articles of manufacture are, in turn, defined as anything made by the hands of humans. In the past, design patents have been granted to items such as truck fenders, chairs, fabric, athletic shoes, toys, tools, and artificial hip joints.

The key to understanding this type of patent is the fact that a patentable design is required to be primarily ornamental and an integral part of an item made by humans.

A design patent provides a 14-year monopoly to industrial designs that have no functional use. That is, contrary to the usefulness rule discussed previously, designs covered by design patents must be purely ornamental. The further anomaly of design patents is that while the design itself must be primarily ornamental, as opposed to primarily functional, it must at the same time be embodied in something human-made. Design patents are easy to apply for, as they do not require much written description. They require drawings for the design, a short description of each figure or drawing, and one claim that says little more than the inventor claims the ornamental design depicted on the attached drawings. In addition, the design patent is less expensive to apply for than a utility patent, lasts for 14 rather than 20 years, and requires no maintenance fees.

20.1.2 The Patent Process

The best method for achieving patentable material is to adequately document your design process as you go through it. Before you begin your project, purchase a composition book (also known as design notebook) with bound pages for keeping your design notes. Start each entry with the date, and include all details of problem identification and solutions. Use drawings or sketches of your idea. Never remove any pages. If you do not like an entry or have made a mistake, simply make an *X* through the entry or write "error." Sign all entries and have a witness sign and date them as frequently as possible. Your witness should be someone you trust who understands your idea and will maintain confidentiality. If you were to do a project on the improvement of an equipment or device, the design process and the related patent information documentation process would consist of the following steps:

- Note all problems caused by equipment, supplies, or nonexisting devices when performing a task.
- Focus on the problem every time you perform the task or use the item.
- Concentrate on solutions.
- Keep a detailed, dated diary of problems and solutions; include drawings and sketches.
- Record the benefits and usefulness of your idea.
- Evaluate the marketability of your idea. If it does not have a wide application, it may be more advantageous to abandon the idea and focus on another.
- Do not discuss your idea with anyone except one person you trust who will maintain confidentiality.
- Prepare an application with a patent attorney.
- Have a search done, first a computer search and then a hand search. It is strongly suggested that the USPTO files, either at the patent office or at various repositories, be consulted.

Be sure to understand your rights as an inventor, as your rights depend on your employment agreement if you are developing patentable material within a company or on your status as a student developing material for hire or for an educational experience (see Section 20.1.4).

Once you have your patent material at hand, you and your advisors (patent lawyer, campus technology transfer office, etc.) must decide between filing a provisional patent and a full patent. A provisional patent allows one a low-cost way of establishing an early "date of filing," allows one to use "Patent Pending" on any literature relating to the design, and may give one the elbow room to determine if there exists a big enough market to make a full patent worthy of pursuit. A written description of your device and drawing (if necessary) are typically all that need to be filed at this point. The provisional patent application has a 1-year lifetime, within which time it must be converted to a complete patent application, or the provisional application is considered abandoned.

Should you pursue a full patent, the patent document that may come of your effort as filed with the Patent and Trademark Office (PTO) will contain the following:

- A title for the invention and the names and addresses of the inventors
- Ownership (assignee) of the patent
- Details of the patent search made by the PTO
- An abstract that concisely describes the key aspects of the invention
- Drawings or flowcharts of the invention
- Very precise definitions of the invention covered by the patent (called the patent claims)
- A brief summary of the invention

Taken together, the various parts of the patent document provide a complete disclosure of every important aspect of the covered invention. When a U.S. patent is issued, all the information in the

patent is readily accessible to the public (worldwide) in the PTO and in patent libraries across the United States and through online patent database services. (Note that the PTO will assist with some simultaneous foreign patent applications.)

As an example, patent number 3,359,806, titled "Multicrystal Tomographic Scanner for Mapping Thin Cross Section of Radioactivity in an Organ of the Human Body" has the following as an abstract: "ABSTRACT: A multicrystal tomographic scanner is utilized for mapping thin slices or cross sections of radioactivity in an organ of the human body which has been injected or injected with a suitable radioisotope. A plurality of radiation detectors are arranged in a cylindrical monoplanar array with each detector focused in such a manner that the fields of view of all of the detectors intersect at a common point, and the detectors are driven mechanically such that this common point of the detectors is caused to move in a rectilinear raster of about 8 inches square. The distribution of radioactivity measured by the detectors due to the amount of radioisotope within the area being scanned is stored in a computer memory and reproduced on an oscilloscope display, as the section is being examined." Section 23.1 will discuss issues relating to this patent further.

U.S. patents are obtained by submitting to the PTO a patent application and an application fee. Once the application is received, the PTO assigns it to an examiner who is supposed to be knowledgeable in the technology underlying the invention. The patent examiner is responsible for deciding whether the invention qualifies for a patent and, assuming it does, what the scope of the patent should be. Usually, back-and-forth communications—called patent prosecution—occur between the applicant and the examiner regarding these issues. Clearly, the most serious and hard-to-fix issue is whether the invention qualifies for a patent.

Eventually, if all of the examiner's objections are overcome by the applicant, the invention is approved for a patent. A patent issue fee is paid, and the applicant receives an official copy of the patent deed. Three additional fees must be paid over the life of the patent to keep it in effect. Note that, though one or more individuals may be listed as inventors, the assignee is the patent holder of record. For the aforementioned patent, four inventors were listed, but the United States Atomic Energy Commission is the assignee, as the invention was done in part with funds from that agency.

20.1.3 Patent Claims

Patent claims are the part of the patent application that precisely limit the scope of the invention—where it begins and where it ends. Perhaps it will help you understand what patent claims do if you analogize them to real estate deeds. A deed typically includes a description of the parcel's parameters precise enough to map the exact boundaries of the plot of land in question, which, in turn, can be used as the basis of a legal action to toss out any trespassers.

In patents, the idea is to similarly draw with the patent claims a clear line around the property of the inventor so that any infringer can be identified and dealt with. Patent claims have an additional purpose. Because of the precise way in which they are worded, claims also are used to decide whether, in light of previous developments, the invention is patentable in the first place.

Unfortunately, to accomplish these purposes, all patent claims are set forth in an odd, stylized format. But the format has a big benefit. It makes it possible to examine any patent application or patent granted by the PTO and get a pretty good idea about what the invention covered by the patent consists of. While the stylized patent claim language and format have the advantage of lending a degree of precision to a field that badly needs it, there is an obvious and substantial downside to the use of the arcane "patentspeak." Mastering it amounts to climbing a fairly steep learning curve.

For the aforementioned patent, there exist 10 claims, which, when coupled with the technical drawings and proof of concept, serve to describe the invention in very fine detail and serve to delimit the range of additional patents that might arise from a study of this particular patent. One claim is, for example, "5. The scanner set forth in claim 4, wherein the number of radiation detectors in said monopolar array is at least eight," would seem to limit one's ability to claim a similar patent with 9 or 10 detectors, for example.

It is when you set out to understand a patent claim that the rest of the patent becomes crucially important. The patent's narrative description of the invention—set out in the patent specification—with all or many of the invention's possible uses, and the accompanying drawings or flowcharts, usually provide enough information in combination to understand any particular claim. And of course, the more patent claims you examine, the more adept you will become in deciphering them.

20.1.4 Protecting Your Rights as an Inventor

As of 2013, the inventor who files the invention first is eligible for the patent; this is the so-called first-to-file rule common in the rest of the world. Whoever files first still must "reduce the invention to practice" to document that the work is theirs. Inventors can reduce the invention to practice in two ways: (1) by making a working model—a prototype—which works as the idea of the invention dictates it should or (2) by constructively reducing it to practice—that is, by describing the invention in sufficient detail for someone else to build it—in a document that is then filed as a patent application with the PTO.

It is often the quality of the inventor's documentation (dated, written in a notebook, showing the conception of the invention and the steps that were taken to reduce the invention to practice) that determines which inventor ends up with the patent.

You especially should be aware that you can unintentionally forfeit your right to obtain patent protection. This can happen if you disclose your invention to others, such as a company interested in the invention, and then do not file an application within 1 year from that disclosure date. Any public disclosure, such as in a speech, poster session, or publication (web or paper) begins a 1-year countdown after which patents are precluded in the United States. The same 1-year period applies if you offer your invention, or a product made by your invention, for sale. You must file your patent application in the United States within 1 year from any offer of sale.

Even more confusing is the fact that most other countries do not allow this 1-year grace period. Any public disclosure before you file your first application will prevent you from obtaining patent protection in nearly every country other than the United States.

20.1.5 Patent Infringement

Patent infringement occurs when someone makes, uses, or sells a patented invention without the patent owner's permission. Defining infringement is one thing, but knowing when it occurs in the real world is something else. Even with common technologies, it can be difficult for experienced patent attorneys to tell whether patents have been infringed.

There are multiple steps in deciding whether infringement of a patent has occurred:

- Identify the patent's independent apparatus and method claims.
- Break these apparatuses and method claims into their elements.
- Compare these elements with the alleged infringing device or process and decide whether the claim has all of the elements that constitute the alleged infringing device or process. If so, the patent has probably been infringed. If not, proceed to the next step.
- If the elements the alleged infringing device or process are somewhat different than the elements of the patent claim, ask if they are the same in structure, function, and result. If yes, you probably have infringement. Note that for infringement to occur, only one claim in the patent needs to be infringed.

A patent's independent claims are those upon which usually one or more claims immediately following depend. A patent's broadest claims are those with the fewest words and that therefore provide the broadest patent coverage. The patent's broadest claims are its independent claims. In order to "infringe a patent," only one of its claims (independent or dependent) need be infringed; it

is not necessary to infringe multiple or all claims. In this sense, each patent claim conveys a stand-alone "patent right."

In apparatus (machine) claims, the elements are usually conceptualized as the (a), (b), (c), and so forth parts of the apparatus that are listed, interrelated, and described in detail following the word "comprising" at the end of the preamble of the claim. Elements in method (process) claims are the steps of the method and subparts of those steps.

If each and every element of the patent's broadest claims is in the infringing device, the patent is probably infringed. The reason you start by analyzing the broadest claim is that by definition, that claim has the fewest elements, and it is therefore easier to find infringements.

Even if infringement cannot be found on the basis of the literal language in the claims, the courts may still find infringement if the alleged infringing device's elements are equivalent to the patent claims in structure, function, and result. Known as the doctrine of equivalents, this rule is difficult to apply in practice.

Defending a patent or initiating a patent infringement lawsuit can be extremely costly; consultation with a good patent lawyer is advised prior to any legal actions. The August 24, 2012, headline "Jury Awards $1 Billion to Apple in Samsung Patent Case" is evidence of the flip side of this fact.

20.1.6 A Word or Four of Warning

In terms of the invention disclosure, irrespective of who goes through the process of obtaining a patent, it is advisable to start by informing the responsible office in your school of your work through an invention disclosure form. Your advisor or supervisor can point you to the correct office where the disclosure form should be submitted. Such a disclosure form typically contains the following sections:

1. Invention title.
2. Inventors name(s), contribution(s), contact information.
3. Applicable contract or grant numbers.
4. Are any IP agreements in place on this work?
5. Were any other parties involved?
6. Earliest date of idea conception.
7. Invention description.
8. Prior disclosures, nature, dates.
9. Invention function (commercial).
10. List of possible licensees.
11. Potential impediments to commercialization of invention.
12. Signatures of inventor(s) and witnesses.

Filling out such a form has several advantages. In addition to helping you think about your invention in a critical manner, it also helps answer ownership questions and provides the basis to determine whether or not to pursue patent protection.

This brings up the question of costs associated with patent protection. Typically, it costs in the neighborhood of $25K to get an allowed U.S. patent; thus, decisions to pursue patents are nontrivial, regardless of who foots the bill. Non-U.S. patent protection can cost significantly more than this, depending primarily on the geographic scope of coverage (six to eight times the U.S. cost). In addition, all patents have to be maintained in good standing by paying periodic fees, which vary with the jurisdiction. Given the associated costs, the decision to proceed with patent protection is primarily based on economic considerations. In an academic setting, the only reason to proceed with a patent is to be able to prevent others from making, using, or selling products and services based on the patent claims in the absence of a license from the academic institution. Thus, an academic institution will base its decisions on the probability of obtaining a license (in a reasonable time frame) on a

patentable invention. In a commercial setting, in addition to providing monopoly, patent protection can also provide a competitive edge.

Two considerations in patents are often comingled and confused; these are inventorship and ownership. In general, it is fair to say that inventorship is a matter of *law*, while ownership is a matter of *contract*. In terms of inventorship, only those individuals who make an "inventive contribution" to one or more claims of a patent are eligible to be inventors. There are several ramifications of this concept.

1. Since claims from some of the original patent application submitters may not eventually issue, thereby preventing some of them from being inventors, strictly speaking, true inventorship can only be determined after patent claims are allowed by the USPTO.
2. An individual needs to be an inventor on a single claim to be a named inventor on the patent.
3. If an individual has proven inventorship and is purposefully denied inventorship status by the other inventors, this is a serious matter and can be grounds for invalidation of an otherwise issued and valid patent.
4. An individual must have inventive contribution to at least one claim in order to be a named inventor in a patent. Simply being the person to state the problem that the patent solves does not make one an inventor; neither does being in a superior or supervisory role in a project or institution.
5. In brief, intentional omission (if he/she had inventive contribution) or inclusion (if he/she did not have inventive contribution) of an inventor could be grounds for eventual invalidation of a technically sound patent.

On the other hand, ownership of a patent is a matter of contract. In other words, the ownership of a patent (assignee) does not necessarily lie with the inventor(s). The ownership can be vested in an employer, research sponsor, or other entity depending on the specific circumstances. In an academic setting, most faculty are required to grant ownership of IP to their parent institution. In the case of students, it is advisable to check the institution's policies; ownership can vary from the inventor to the institution depending on the specifics of the circumstances. These rules and policies are usually available on the university's website.

20.2 COPYRIGHTS

A copyright is a legal right that provides the creator of a work of authorship the right to control how the work is used. If someone wrongfully uses material covered by a registered copyright, the copyright owner can sue and obtain compensation for any losses suffered, as well as an injunction requiring the copyright infringer to stop the infringing activity.

A copyright is a type of tangible property. It belongs to its owner, and the courts can be asked to intervene if anyone uses it without permission. Like other forms of property, a copyright may be sold by its owner or otherwise exploited by the owner for economic benefit.

The Copyright Act of 1976 grants creators many intangible, exclusive rights over their work, including reproduction rights—the right to make copies of a protected work; distribution rights—the right to sell or otherwise distribute copies to the public; the right to create adaptations—the right to prepare new works based on the protected work; and performance and display rights—the right to perform a protected work or display a work in public. Copyright law is evolving; the most recent revisions occurred in 1998.

Copyright protects all varieties of original works of authorship, including the following:

- Literary works
- Motion pictures, videos, and other audiovisual works

- Photographs, sculpture, and graphic works
- Sound recordings
- Pantomimes and choreographic works
- Architectural works

20.2.1 What Can Be Copyrighted?

Not every work of authorship receives copyright protection. A program or other work is protected if it satisfies all three of the following requirements:

- Fixation
- Originality
- Minimal creativity

The work must be fixed in a tangible medium of expression. Any stable medium from which the work can be read back or heard, either directly or with the aid of a machine or device, is acceptable.

Copyright protection begins the instant you fix your work. There is no waiting period, and it is not necessary to register the copyright. Copyright protects both completed and unfinished works, as well as works that are widely distributed to the public or never distributed at all.

A work is protected by copyright only if, and to the extent that, it is original. But this does not mean that copyright protection is limited to works that are novel—that is, new to the world. For copyright purposes, a work is "original" if at least a part of the work owes its origin to the author. A work's quality, ingenuity, aesthetic merit, or uniqueness is not considered.

A minimal amount of creativity over and above the independent creation requirement is necessary for copyright protection. Works completely lacking creativity are denied copyright protection even if they have been independently created. However, the amount of creativity required is very slight.

It is important to recognize that, unlike patent protection, copyright protection extends only to the *expression* of the idea and not the idea itself.

In the past, some courts held that copyright protected works that may have lacked originality and/or creativity if a substantial amount of work was involved in their creation. Recent court cases have outlawed this "sweat of the brow" theory. It is now clear that the amount of work put in to create a work of authorship has absolutely no bearing on the degree of copyright protection it will receive. Copyright only protects fixed, original, minimally creative expressions, not hard work.

Perhaps the greatest difficulty with copyrights is determining just what aspects of any given work are protected. All works of authorship contain elements that are protected by copyright and elements that are not protected. Unfortunately, there is no system available to precisely identify which aspects of a given work are protected. The only time we ever obtain a definitive answer as to how much any particular work is protected is when it becomes the subject of a copyright infringement lawsuit. However, there are two tenets that may help in determining what is protected and what is not. The first tenet states that a copyright only protects "expressions," not ideas, systems, or processes. Tenet two states that the scope of copyright protection is proportional to the range of expression available. Let us look at both in detail.

Copyright only protects the tangible expression of an idea, system or process—not the idea, system, or process itself. Copyright law does not protect ideas, procedures, processes, systems, mathematical principles, formulas, titles, algorithms, methods of operation, concepts, facts, and discoveries. Remember, copyright is designed to aid the advancement of knowledge. If the copyright law gave a person a legal monopoly over ideas, the progress of knowledge would be impeded rather than helped.

The scope of copyright protection is proportional to the range of expression available. The copyright law only protects original works of authorship. Part of the essence of original authorship is

the making of choices. Any work of authorship is the end result of a whole series of choices made by its creator. For example, the author of a novel expressing the idea of love must choose the novel's plot, characters, locale, and the actual words used to express the story. The author of such a novel has a nearly limitless array of choices available. However, the choices available to the creators of many works of authorship are severely limited. In these cases, the idea or ideas underlying the work and the way they are expressed by the author are deemed to "merge." The result is that the author's expression is either treated as if it were in the public domain or protected only against virtually verbatim or "slavish" copying.

20.2.2 The Copyright Process

20.2.2.1 Copyright Notice

Before 1989, all published works had to contain a copyright notice (the "©" symbol followed by the publication date and copyright owner's name) to be protected by copyright. This is no longer necessary. Use of copyright notices is now optional in the United States. Even so, it is always a good idea to include a copyright notice on all work distributed to the public so that potential infringers will be informed of the underlying claim to copyright ownership. In addition, copyright protection is not available in some 20 foreign countries unless a work contains a copyright notice.

There are strict technical requirements as to what a copyright notice must contain. A valid copyright must contain three elements:

- *The copyright symbol*—use the familiar "©" symbol, that is, the lowercase letter "c" completely surrounded by a circle. The word "Copyright" or the abbreviation "Copr." is also acceptable in the United States but not in many foreign countries. So if your work might be distributed outside the United States, always use the "©" symbol.
- *The year in which the work was published*—you only need to include the year the work was first published.
- *The name of the copyright owner*—the owner is (1) the author or authors of the work, (2) the legal owner of a work made for hire, or (3) the person or entity to whom all the author's exclusive copyright rights have been transferred.

Although the three elements of a copyright notice need not appear in a particular order, it is common to list the copyright symbol, followed by the date and owners. It is also advisable to include "All Rights Reserved."

According to Copyright Office regulations, the copyright notice must be placed so as not to be concealed from an ordinary user's view upon reasonable examination. A proper copyright notice should be included on all manuals and promotional materials. Notices on written works are usually placed on the title page or the page immediately following the title page.

20.2.2.2 Copyright Registration

Copyright registration is a legal formality by which a copyright owner makes a public record in the U.S. Copyright Office in Washington, DC (a part of the U.S. Library of Congress), of some basic information about a protected work, such as the title of the work, who wrote it and when, and who owns the copyright. It is not necessary to register to create or establish a copyright. Since original works are born copyrighted, registration of copyright is optional. However, in order to take legal action claiming copyright infringement, a copyright must be registered prior to filing such a suit.

Copyright registration is a relatively easy process. You must fill out the appropriate preprinted application form, pay an application fee, and mail the application and fee to the Copyright Office in Washington, DC, along with two copies of the work being registered.

20.2.3 Copyright Duration

One of the advantages of copyright protection is that it lasts a very long time. The copyright in a protectable work created after 1977 by an individual creator lasts for the life of the creator plus an additional 70 years. If there is more than one creator, the life-plus-70-year term is measured from the date the last creator dies. Many classical novels are now out of copyright and may be found in the public domain. The copyright in works created by employees for their employers last for 95 years from the date of publication, or 120 years from the date of creation, whichever occurs first.

20.2.4 Protecting Your Copyright Rights

The exclusive rights granted by the Copyright Act initially belong to a work's author. There are four ways to become an author:

- An individual may independently author a work.
- An employer may pay an employee to create the work, in which case the employer is the author under the work-made-for-hire rule.
- A person or business entity may specially commission an independent contractor to create the work under a written-work-made-for-hire contract, in which case the commissioning party becomes the author.
- Two or more individuals or entities may collaborate to become joint authors.

The initial copyright owner of a work is free to transfer some or all copyright rights to other people or businesses, who will then be entitled to exercise the rights transferred.

20.2.5 Infringement

Copyright infringement occurs when a person other than the copyright owner exploits one or more of the copyright owner's exclusive rights without the owner's permission. A copyright owner who wins an infringement suit may stop any further infringement, obtain damages from the infringer, and recover other monetary losses. This means, in effect, that a copyright owner can make a copyright infringer restore the author to the same economic position they would have been in had the infringement never occurred. In order to file copyright infringement suits in the federal courts, one must have a registered copyright. In addition, registration of copyright offers the possibility of significantly higher damage awards. Copyright infringement is usually proven by showing that the alleged infringer had access to the copyright owner's work and that the protected expression in the two works is substantially similar. In recent years, the courts have held that the person who claims his/her work was infringed upon must subject his/her work to a rigorous filtering process to find out which elements of the work are and are not protected by copyright. In other words, the plaintiff must filter out from his work idea elements dictated by efficiency or external factors or taken from the public domain. After this filtration process is completed, there may or may not be any protectable expression left.

20.3 TRADEMARKS

A trademark is a work, name, symbol, or a combination used to identify the source of goods and services and also distinguish them from others. Trademark rights continue indefinitely as long as the mark is not abandoned and is properly used.

A federal trademark registration is maintained by filing a declaration of use during the sixth year after its registration and by renewal every 20 years, as long as the mark is still in use. The federal law provides that nonuse of a mark for 2 consecutive years is ordinarily considered abandonment,

and the first subsequent user of the mark can claim exclusive trademark rights. Trademarks, therefore, must be protected, or they will be lost. They must be distinguished in print form from other words and must appear in a distinctive manner.

Trademarks should be followed by a notice of their status. If it has been registered in the USPTO, the registration notice "®" or "Reg. U.S. Pat Off" should be used. Neither should be used, however, if the trademark has not been registered, but the superscripted letters "TM" should follow the mark, or an asterisk can be used to refer to a footnote stating "a trademark of xxx." The label compliance manager should remember that trademarks are proper adjectives and must be accompanied by the generic name for the product they identify. Trademarks are not to be used as possessives, not in the plural form.

A trademark is any visual mark that accompanies a particular tangible product, or line of goods, and serves to identify and distinguish it from products sold by others, and it indicates its source. A trademark may consist of letters, words, names, phrases, slogans, numbers, colors, symbols, designs, or shapes. As a general rule, to be protected from unauthorized use by others, a trademark must be distinctive in some way.

The word "trademark" is also a generic term used to describe the entire broad body of state and federal law that covers how businesses distinguish their products and services from the competition. Each state has its own set of laws establishing when and how trademarks can be protected. There is also a federal trademark law, called the Lanham Act, which applies in all 50 states. Generally, state trademark laws are relied upon for marks used only within one particular state, while the Lanham Act is used to protect marks for products that are sold in more than one state or across territorial or national borders.

20.3.1 Selecting a Trademark

Not all trademarks are treated equally by the law. The best trademarks are "distinctive"—that is, they stand out in a customer's mind because they are inherently memorable. The more distinctive the trademark is, the stronger it will be, and the more legal protection it will receive. Less distinctive marks are "weak" and may be entitled to little or no legal protection.

Generally, selecting a mark begins with brainstorming for general ideas. After several possible marks have been selected, the next step is often to use formal or informal market research techniques to see how the potential marks will be accepted by customers. Next, a "trademark search" is conducted. This means that an attempt is made to discover whether the same or similar marks are already in use.

20.3.1.1 What Is a Distinctive Trademark?

A trademark should be created that is distinctive rather than descriptive. A trademark is "distinctive" if it is capable of distinguishing the product to which it is attached from competing products. Certain types of marks are deemed to be inherently distinctive and are automatically entitled to maximum protection. Others are viewed as not inherently distinctive and can be protected only if they acquire "secondary meaning" through use.

Arbitrary, fanciful, or coined marks are deemed to be inherently distinctive and are therefore very strong marks. These are words and/or symbols that have absolutely no meaning in the particular trade or industry prior to their adoption by a particular manufacturer for use with its goods or services. After use and promotion, these marks are instantly identified with a particular company and product, and the exclusive right to use the mark is easily asserted against potential infringers.

Fanciful or arbitrary marks consist of common words used in an unexpected or arbitrary way so that their normal meaning has nothing to do with the nature of the product or service they identify. Some examples would be *Apple computer* and *Peachtree software*.

Coined words are words made up solely to serve as trademarks, such as *ZEOS* or *Intel*.

Suggestive marks are also inherently distinctive. A suggestive mark indirectly describes the product it identifies but stays away from literal descriptiveness. That is, the consumer must engage in a mental process to associate the mark with the product it identifies. For example, *WordPerfect* and *VisiCalc* are suggestive marks.

Descriptive marks are not considered to be inherently distinctive. They are generally viewed by the courts as weak and thus not deserving of much, if any, judicial protection unless they acquire a "secondary meaning"—that is, become associated with a product in the public's mind through long and continuous use. There are three types of descriptive marks: (1) marks that directly describe the nature or characteristics of the product they identify (for example, *Quick Mail*), (2) marks that describe the geographic location from which the product emanates (for example, *Oregon software*), and (3) marks consisting primarily of a person's last name (for example, *Norton Utilities*). A mark that is in continuous and exclusive use by its owner for a 5-year period is presumed to have acquired secondary meaning and qualifies for registration as a distinctive mark.

A generic mark is a word(s) or symbol that is commonly used to describe an entire category or class of products or services, rather than to distinguish one product or service from another. Generic marks are in the public domain and cannot be registered or enforced under the trademark laws. Some examples of generic marks include "computer," "mouse," and "RAM." A term formerly protected as a trademark may lose such protection if it becomes generic. This often occurs when a mark is assimilated into common use to such an extent that it becomes the general term describing an entire product category. Examples would be *escalator* and *Xerox*. Copyright owners must be vigilant against their trademarks becoming generic terms (e.g., *Hoover* implying vacuum cleaners, *Kleenex* implying facial tissue); recovery from becoming generic terms can be costly in time and money.

It is interesting that certain sounds can be the subject of trademark protection. For example, one hears the distinctive roar of the MGM lion, the three-note sequence chimes of NBC, and the up-tempo beats of SportsCenter.

20.3.2 The Trademark Process

A trademark is registered by filing an application with the USPTO in Washington, DC. Registration is not mandatory. Under both federal and state law, a company may obtain trademark rights in the states in which the mark is actually used. However, federal registration provides many important benefits, including the following:

- The mark's owner is presumed to have the exclusive right to use the mark nationwide.
- Everyone in the country is presumed to know that the mark is already taken.
- The trademark owner obtains the right to put an "®" after the mark.
- Anyone who begins using a confusingly similar mark after the mark has been registered will be deemed a willful infringer.
- The trademark owner obtains the right to make the mark "incontestable" by keeping it in continuous use for 5 years.

To qualify for federal trademark registration, a mark must meet several requirements. The mark must

- Actually be used in commerce
- Be sufficiently distinctive to reasonably operate as a product identifier
- Not be confusingly similar to an existing, federally registered trademark

A mark you think will be good for your product could already be in use by someone else. If your mark is confusingly similar to one already in use, its owner may be able to sue you for trademark infringement and get you to change it and even pay damages. Obviously, you do not want to spend

time and money marketing and advertising a new mark only to discover that it infringes on another preexisting mark and must be changed. To avoid this, state and federal trademark searches should be conducted to attempt to discover if there are any existing similar marks. You can conduct a trademark search yourself, either manually or with the aid of computer databases. You may also pay a professional search firm to do so (advisable).

It is worth noting that the same mark can be used for completely different classes of products and services.

20.3.3 Intent to Use Registration

If you seriously intend to use a trademark on a product in the near future, you can reserve the right to use the mark by filing an intent-to-use registration. If the mark is approved, you have 6 months to actually use the mark on a product sold to the public. If necessary, this period may be increased by 6-month intervals up to 24 months if you have a good explanation for the delay. No one else may use the mark during this interim period. You should promptly file an intent-to-use registration as soon as you have definitely selected a trademark for a forthcoming product.

20.3.4 Protecting Your Trademark Rights

The owner of a valid trademark has the exclusive right to use the mark on its products and in related advertising or marketing. Depending on the strength of the mark and whether and where it has been registered, the trademark owner may be able to bring a court action to prevent others from using the same or similar marks on competing or related products. (For example, Johnson and Johnson has as its trademark the red cross on all of its products.)

Trademark infringement occurs when an alleged infringer uses a mark that is likely to cause consumers to confuse the infringer's products with the trademark owner's products. A mark need not be identical to one already in use to infringe upon the owner's rights. If the proposed mark is similar enough to the earlier mark to risk confusing the average consumer, its use will constitute infringement.

Determining whether an average consumer might be confused is the key to deciding whether infringement exists. The determination depends primarily on whether the products or services involved are related and, if so, whether the marks are sufficiently similar to create a likelihood of consumer confusion.

If a trademark owner is able to convince a court that infringement has occurred, he/she may be able to get the court to order the infringer to stop using the infringing mark and to pay monetary damages. Depending on whether the mark was registered, such damages may consist of the amount of the trademark owner's losses caused by the infringement or the infringer's profits. In cases of willful infringement, the courts may double or triple the damages award.

A trademark owner must be assertive in enforcing its exclusive rights. Each time a mark is infringed upon, it loses strength and distinctiveness and may eventually die by becoming generic.

20.4 TRADE SECRETS

Trade secrecy is basically a do-it-yourself form of IP protection. It is based on the simple idea that by keeping valuable information secret, one can prevent competitors from learning about and using it. Trade secrecy is by far the oldest form of IP, dating back at least to ancient Rome. It is as useful now as it was then.

A trade secret is any formula, pattern, physical device, idea, process, compilation of information, or other information that (1) is not generally known by a company's competitors, (2) provides a business with a competitive advantage, and (3) is treated in a way that can reasonably be expected to prevent the public or competitors from learning about it, absent improper acquisition or theft.

Trade secrets may be used to do the following:

- Protect ideas that offer a business a competitive advantage
- Keep competitors from knowing that a program is under development and from learning its functional attributes
- Protect source code, software development tools, design definitions and specifications, manuals, and other documentation
- Protect valuable business information such as marketing plans, cost and price information, and customer lists

Unlike copyrights and patents, whose existence is provided and governed by federal law that applies in all 50 states, trade secrecy is not codified in any federal statute. Instead, it is made up of individual state laws. Nevertheless, the protection afforded to trade secrets is much the same in every state. This is partly because some 47 states (and the District of Columbia, Puerto Rico, and the U.S. Virgin Islands) have based their trade secrecy laws on the Uniform Trade Secrets Act (1985), a model trade secrecy law designed by legal scholars.

20.4.1 What Qualifies for Trade Secrecy?

Information that is public knowledge or generally known cannot be a trade secret. Things that everybody knows cannot provide anyone with a competitive advantage. However, information comprising a trade secret need not be novel or unique. All that is required is that the information not be generally known by people who could profit from its disclosure and use.

20.4.2 Trade Secrecy Authorship

Only the person who owns a trade secret has the right to seek relief in court if someone else improperly acquires or discloses the trade secret. Only the trade secret owner may grant others a license to use the secret.

As a general rule, any trade secrets developed by an employee in the course of employment belong to the employer. However, trade secrets developed by employees on their own time and with their own equipment can sometimes belong to the employee. To avoid possible disputes, it is a very good idea for employers to have all the employees who may develop new technology sign an employment agreement that assigns in advance all trade secrets developed by employees during their employment to the company.

20.4.3 How Trade Secrets Are Lost

A trade secret is lost if the product in which it is embodied is made widely available to the public through sales or displays on an unrestricted basis, or the secret can be discovered by reverse engineering or inspection. One critical disadvantage of trade secrecy as a form of IP protection is the concept of irretrievability; that is, once the secret is divulged/known, the rights associated with it cannot be retrieved.

20.4.4 Duration of Trade Secrets

Trade secrets have no definite term. A trade secret continues to exist as long as the requirements for trade secret protection remain in effect. In other words, as long as secrecy is maintained, the secret does not become generally known in the industry, and the secret continues to provide a competitive advantage, it will be protected.

20.4.5 Protecting Your Trade Secret Rights

A trade secret owner has the legal right to prevent the following two groups of people from using and benefiting from its trade secrets or disclosing them to others without the owner's permission:

- People who are bound by a duty of confidentiality not to disclose or use the information
- People who steal or otherwise acquire the trade secret through improper means

A trade secret owner's rights are limited to these two restricted groups of people. In this respect, a trade secret owner's rights are much more limited than those of a copyright owner or patent holder.

Trade secret owners may enforce their rights by bringing a trade secret infringement action in court. Such suits may be used to do the following:

- Prevent another person or business from using the trade secret without proper authorization
- Collect damages for the economic injury suffered as a result of the trade secret's improper acquisition and use

All persons responsible for the improper acquisition and all those who benefited from the acquisition are typically named as defendants in trade secret infringement actions. To prevail in a trade secret infringement suit, the plaintiff must show that the information alleged to be secret is actually a trade secret. In addition, the plaintiff must show that the information was either improperly acquired by the defendant or improperly disclosed, or likely to be so, by the defendant.

There are two important limits on trade secret protection. It does not prevent others from discovering a trade secret through reverse engineering, nor does it apply to persons who independently create or discover the same information.

20.4.6 A Trade Secrecy Program

The first step in any trade secret protection program is to identify exactly what information and material is a company trade secret. It makes no difference in what form a trade secret is embodied. Trade secrets may be stored on computer hard disks or floppies, written down, or exist only in employees' memories.

Once a trade secret has been established, the protection program should include the following steps:

- Maintain physical security.
- Enforce computer security.
- Mark confidential documents "confidential."
- Use nondisclosure agreements.

Nondisclosure agreements are generally simple documents that indicate that you will be(come) privy to some knowledge about a product, information/data, or procedure. Minimal documents basically indicate, "The undersigned reader acknowledges that the information provided by XXX Inc. in these product declarations is confidential; therefore, the reader agrees not to disclose it without the express written permission of XXX Inc. or YYY, director of XXX. It is acknowledged by reader that information to be furnished in these product requirements is confidential in nature, other than that which is in the public domain through others means and that any disclosure or use of same by reader may cause harm to XXX, Inc." This section would typically be signed and dated by you, the one who is seeking the information.

A nondisclosure agreement is a legal document. Be sure to understand your company/university policies on this matter.

20.4.7 Use of Trade Secrecy with Copyrights and Patents

Trade secrecy is a vitally important protection for some medical device developments, but because of its limitations listed prior, it should be used in conjunction with copyright and, in some cases, patent protection.

20.4.7.1 Trade Secrets and Patents

The federal patent laws provide the owner of a patentable invention with far greater protection than that available under trade secrecy laws. Trade secret protection is not lost when a patent is applied for. The patent office keeps patent applications confidential unless or until a patent is granted. However, once a patent is granted and an issue fee paid, the patent generally becomes public record. Then all the information disclosed in the patent application is no longer a trade secret. This is so even if the patent is later challenged in court and invalidated.

If, for example, a software program is patented, the software patent applies only to certain isolated elements of the program. The remainder need not be disclosed in the patent and can remain a trade secret.

20.4.7.2 Trade Secrets and Copyrights

Trade secrecy and copyright are not incompatible. To the contrary, they are typically used in tandem to provide the maximum legal protection available.

20.5 LICENSING

Patents, trademarks, and copyrights are legal terms in most societies. If the owner wishes to quickly gain financial return on this property, either a sale of the property outright or a licensing of the rights to use the property is necessitated. The benefits of a sale versus a licensing of the property must be considered. For a small firm or individual, the sale option often is best, considering that most inventions involve further development and refining (and thus financial backing) prior to a net return on investment. For a large firm or university, the decision may be made based upon a sale versus a multiyear return-on-investment calculation. Good advice at this point will be needed for a correct decision.

Licensing is an option, for example, for 224 patents of 853 held at Vanderbilt University in a December 2013 website statistic for their Center for Technology Transfer and Commercialization (http://www.vanderbilt.edu/cttc/). Licensing grants a licensee the right to use the specified IP for a given length of time, perhaps modified by the right to use it in a specific area (such as South America) for a specified monetary or other fee. Properly written, the legal documents can force the return of the IP if payments or other conditions are not met. If the commercialization team is successful, the returns on licensed property may exceed that of outright sales and thus will benefit both the inventor and his/her university in the long run. Sometimes it is better to be able to pay one time for a new roof, however, than to yearly pay the maintenance on your auto (King).

EXERCISES

1. What are the basic differences between a patent, a copyright, and a trademark? (To include: brief definition, rights included/excluded, lifespan of each.)
2. Give a specific example of material in which the creator would seek a patent, a copyright, and a trademark.
3. One method of patent searching is to sift through the many patents in the United States Patent and Technology Office (USPTO) database. Go to http://www.uspto.gov. Do a patent search of a medical device of your choice. Write a brief summary of your search information. Of the six types of subject matter included under a patent, under which category can

your material be classified? (Summary to include: exact definition of the item patented, who patented the device, application number, and date filed.) Hint: There are many ways to do a search on the USPTO home page. One way is to click on Patents, then Issued Years and Patent Numbers, Search, Patent Database, Boolean, and then enter MEDICAL into the query. However, you are not bound by these steps to search the database!

4. What are some alternatives to this method (sifting through the USPTO home page) of patent searching?
5. Do a U.S. patent search using your last name as a search term. Write up a patent found (no result, use Smith). What does it do?
6. Do a copyright search similar to question 4.
7. One of the authors of this text holds patent number 3,591,806. How many other patents refer to this patent as prior art?
8. Draft an IP agreement with your advisor. Draft an IP disclosure for your work.
9. Outline your patent application for your design project.
10. Find and briefly report on the topics of "service marks" and "mask works."

ACKNOWLEDGMENT

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21 Manufacturing and Quality Control

Amateurs work until they get it right. Professionals work until they can't get it wrong.

Anonymous

The Food and Drug Administration (FDA) promulgated the good manufacturing practices (GMPs) for medical devices regulations in 1978, drawing authority from the Medical Devices Amendments to the Federal Food, Drug, and Cosmetic (FD&C) Act of 1976. The GMP regulations represented a total quality assurance program intended to control the manufacture and distribution of devices. It allows the FDA to periodically inspect medical device manufacturers for compliance to the regulations.

Manufacturers must operate in an environment in which the manufacturing process is controlled. Manufacturing excellence can only be achieved by designing products and processes to address potential problems before they occur. Manufacturers must also operate in an environment that meets GMP regulations. This requires proof of control over manufacturing processes.

21.1 A HISTORY OF GMPs

Two years after the Medical Device Amendments of 1976 were enacted, the FDA issued its final draft of the medical device GMP regulation, a series of requirements that prescribed the facilities, methods, and controls to be used in the manufacturing, packaging, and storage of medical devices. Except for an update of organizational references and revisions to the critical device list included in the 1978 final draft's preamble, these regulations have remained virtually unchanged since they were published in the *Federal Register* on July 21, 1978. That does not mean that their interpretation has not changed.

Several key events since that date have influenced the way the FDA has interpreted and applied these regulations. The first occurred in 1987 with the FDA's publication of the "Guidelines on General Principles of Process Validation," which not only provided guidance but also advised industry that device manufacturers must validate other processes when necessary to assure that these processes would consistently produce acceptable results.

In 1989, the FDA published a notice of availability for design control recommendations titled "Preproduction Quality Assurance Planning: Recommendations for Medical Device Manufacturers." These recommendations fulfilled a promise made by the Center for Devices and Radiological Health (CDRH) director to a congressional hearing committee to do something to prevent device failures that were occurring due to design defects, resulting in some injuries and deaths. It was also a warning to industry that the FDA was moving to add design controls to the GMP regulation.

The next year, the FDA moved closer to adding design controls, publishing the "Suggested Changes to the Medical Device Good Manufacturing Practices Regulation Information Document," which described the changes the agency was proposing to make to the GMP regulation. Comments asserted that the FDA did not have the authority to add design controls to the GMPs, a point that became moot later that year when the Safe Medical Devices Act of 1990 (SMDA) became law. The SMDA amended section 520(f) of the FD&C Act to add "preproduction design validation" controls to the device GMP regulation.

The SMDA also added to the FD&C Act a new section, 803, which encouraged the FDA to work with foreign countries toward mutual-recognition agreements for the GMP and other regulations. Soon afterward, the FDA began to actively pursue the harmonization of GMP requirements on a global basis.

Over the following 2 years, the FDA took steps to assure that manufacturers with device applications under review at the agency were also in compliance with GMPs. The first step was taken in 1991, when CDRH established its "reference list" program for manufacturers with pending premarket approval (PMA) applications, ensuring that no PMA would be approved while the device maker had significant GMP violations on record. In 1992, the program was extended to all 510(k)s. Under this umbrella program, 510(k)s would not be processed if there was evidence on hand that the site where the 510(k) device would be manufactured was not in compliance with GMPs.

On November 23, 1993, the FDA acted on comments it had received 3 years earlier regarding its "Suggested Changes" document, publishing a proposed revision of the 1978 GMPs in the *Federal Register*. The proposal incorporated almost all of the 1987 version of ISO 9001, the quality systems standard compiled by the International Organization for Standardization. While supporting adoption of ISO 9001, most of the comments received from industry objected to the addition of proposals such as applying the GMP regulation to component manufacturers.

In July 1995, the FDA published a working draft of the proposed final revised GMP regulation. As stated in that draft, the two reasons for the revision were to bring about the addition of design and servicing controls and to ensure that the requirements were made compatible with those of ISO 9001 and EN46001 (ISO 13485), the quality standard that manufacturers must meet if they select the European Union directives' total quality system approach to marketing.

Among the proposals in this version that drew the most fire from industry were the application of GMPs to component manufacturers and use of the term *end of life*, which was intended to differentiate between servicing and reconditioning. The FDA agreed to delete most but not all of the objectionable requirements during an August 1995 FDA–industry meeting and the GMP Advisory Committee meeting in September, 1995. The end-of-life concept was deleted from the GMPs but was retained in the medical device reporting regulation.

In addition, the FDA has indicated that GMP inspections might be made by third parties. If that happens, these inspections would probably begin on a small scale. But eventually, third parties could play an important role in mitigating delays from the FDA's reference list, which, while not now referred to by that name, is still in effect and not likely to be dropped by the agency. Although review of a 510(k) is not affected by the manufacturer being on the list, a 510(k) will not be approved until the manufacturing site is found to be in GMP compliance. The availability of the third-party auditors to inspect those sites might speed up the review process under those circumstances.

21.2 THE GMP REGULATION

The GMP regulations were established to replace quality assurance program requirements with quality system requirements that include design, purchasing, and servicing controls; clarify record-keeping requirements for device failure and complaint investigations; clarify requirements for qualifying, verifying, and validating processes and specification changes; and clarify requirements for evaluating quality data and correcting quality problems. In addition, the FDA has also revised the current good manufacturing practice (CGMP) requirements for medical devices to assure they are compatible with specifications for quality systems contained in international quality standard ISO 9001. This revision was published on October 7, 1996 (61FR52602), and went into effect June 1, 1997.

The following changes were made from previous regulations.

21.2.1 Design Controls

Over the past several years, the FDA has identified lack of design controls as one of the major causes of device recalls. The intrinsic quality of devices, including their safety and effectiveness, is established during the design phase. The FDA believes that unless appropriate design controls are observed during preproduction stages of development, a finished device may be neither safe nor effective for its intended use. This has added general requirements for design controls to the device CGMP regulations for all Class III and II devices and several Class I devices.

21.2.2 Purchasing Controls

The quality of purchased products and services is crucial to maintaining the intrinsic safety and effectiveness of a device. Many device failures due to problems with components that result in recall are due to unacceptable components provided by suppliers. The FDA has found during CGMP inspections that the use of unacceptable components is often due to the failure of the manufacturer of finished devices to adequately establish and define requirements for the device's purchased components, including quality requirements. Therefore, the FDA believes that the purchasing of components, finished devices, packaging, labeling, and manufacturing materials must be conducted with the same level of planning, control, and verification as internal activities. The FDA believes that the appropriate level of control should be achieved through a proper mixture of supplier and in-house controls.

21.2.3 Servicing Controls

The FDA has found, as a result of reviewing service records, that the data resulting from the maintenance and repair of medical devices provide valuable insight into the adequacy of the performance of devices. Thus, the FDA believes that service data must be included among the data manufacturers use to evaluate and monitor the adequacy of the device design, the quality system, and the manufacturing process. Accordingly, the FDA has added general requirements for the maintenance of servicing records and for the review of these records by the manufacturer. Manufacturers must assure that the performance data obtained as a part of servicing product are fed back into the manufacturer's quality system for evaluation as part of the overall device experience data.

21.2.4 Changes in Critical Device Requirements

The FDA has eliminated the critical component and critical operation terminology contained in the CGMP regulation. The increased emphasis on purchasing controls and on establishing the acceptability of component suppliers assures that the intent of the critical component requirement is carried forward. The addition of a requirement to validate and document special processes further ensures that the requirements of the critical operation are retained. The FDA has retained the distinction between critical and noncritical devices for one regulatory purpose. Traceability will continue to be required only for critical devices.

21.2.5 Harmonization

The FDA has reorganized the structure of the device CGMP regulations and modified some of their language in order to harmonize with international quality standards. The FDA has relocated and combined certain requirements to better harmonize the requirements with specifications for quality systems in the ISO 9001 quality standard and to use as much common language as possible to enhance conformance with ISO 9001 terminology. By requiring all manufacturers to design and manufacture devices under the controls of a total quality system, the FDA believes this will improve the quality of medical devices manufactured in the United States for domestic distribution or exportation as well as

devices imported from other countries. The changes should ensure that only safe and effective devices are distributed, in conformance with the act. Harmonization means a general enhancement of CGMP requirements among the world's leading producers of medical devices.

21.3 DESIGN FOR MANUFACTURABILITY

Design for manufacturability (DFM) assures that a design can be repeatably manufactured while satisfying the requirements for quality, reliability, performance, availability, and price. One of the fundamental principles of DFM is reducing the number of parts in a product. Existing parts should be simple and add value to the product. All parts should be specified, designed, and manufactured to allow 100% usable parts to be produced. It takes a concerted effort by design, manufacturing, and vendors to achieve this goal.

DFM is desirable because it is less costly. The reduction in cost is due to the following:

- A simpler design with fewer parts
- Simple production processes
- Higher quality and reliability
- Ease of servicing

21.3.1 The DFM Process

The theme of DFM is to eliminate nonfunctional parts, such as screws or fasteners, while also reducing the number of functional parts. The remaining parts should each perform as many functions as possible. The following questions help in determining if a part is necessary:

- Must the part move relative to its mating part?
- Must the part be of a different material than its mating part or isolated from all other parts?
- Must the part be separate for disassembly or service purposes?

All fasteners are automatically considered candidates for elimination.

A process that can be expected to have a defect rate of no more than a few parts per million (such as a Six Sigma process) consists of the following:

- Identification of critical characteristics
- Determining product elements contributing to critical characteristics
- For each identified product element, determining the step or process choice that affects or controls required performance
- Determining a nominal value and maximum allowable tolerance for each product component and process step
- Determining the capability for parts and process elements that control required performance
- Assure that the capability index (Cp) is greater than or equal to 2, where

$$Cp = (\text{specification width})/\text{process capability}$$

21.4 DESIGN FOR ASSEMBLY

Design for assembly (DFA) is a structured methodology for analyzing product concepts or existing products for simplification of the design and its assembly process. Reduction in parts and assembly operations and individual-part geometry changes to ease assembly are the primary goals. The analysis process exposes many other life cycle cost and customer satisfaction issues, which can then be addressed. Design and assembly process quality are significantly improved by this process.

Most textbook approaches to DFA discuss elimination of parts. While this is a very important aspect of DFA, there are also many other factors that affect product assembly. A few rules include the following:

- Overall design concept
  - The design should be simple with a minimum number of parts.
  - Assure that the unit is lightweight.
  - The system should have a unified design approach, rather than look like an accumulation of parts.
  - Components should be arranged and mounted for the most economical assembly and wiring.
  - Components that have a limited shelf life should be avoided.
  - The use of special tools should be minimized.
  - The use of wiring and harnesses to connect components should be avoided.
- Component mounting
  - The preferred assembly direction is top-down.
  - Repositioning of the unit to different orientations during assembly should be avoided.
  - All functional internal components should mount to one main chassis component.
  - Mating parts should be self-aligning.
  - Simple, foolproof operations should be used.
- Test points
  - Pneumatic test point shall be accessible without removal of any other module.
  - Electrical test points shall include, but not be limited to the following:
    - Reference voltages.
    - Adjustments.
    - Key control signals.
    - Power supply voltages.
    - All electronic test points shall be short-circuit protected and easily accessible.
- Stress levels and tolerances
  - The lowest possible stress levels should be used.
  - The maximum possible operating limits (OLs) and mechanical tolerances should be maximized.
  - Operations of known capability should be used.
- Printed circuit boards (PCBs)
  - Adequate clearance should be provided around circuit board mounting locations to allow for tools.
  - Components should be soldered, not socketed.
  - PCBs must be mechanically secured and supported.
  - There must be unobstructed access to test and calibration points.
  - Exposed voltages should be less than 40 volts.
- Miscellaneous
  - All air intakes should be filtered, and an indication that the filter needs to be changed should be given to the user.
  - The device shall be packed in a recyclable container so as to minimize the system installation time.

21.4.1 Design for Assembly Process

Develop a multifunctional team before the new product architecture is defined. This team should foster a creative climate that will encourage ownership of the new product's design and delivery process.

Establish product goals through a benchmarking process or by creating a model, drawing, or conception of the product.

Perform a DFA analysis of the product. This identifies possible candidates for elimination or redesign, as well as highlighting high-cost assembly operations.

Segment the product architecture into manageable modules or levels of assembly.

Apply DFA principles to these assembly modules to generate a list of possible cost opportunities.

Apply creative tools, such as brainstorming, to enhance the emerging design and identify further design improvements.

As a team, evaluate and select the best ideas, thus narrowing and focusing the team's goals.

Make commodity and material selections. Start early supplier involvement to assure economical production.

With the aid of cost models or competitive benchmarking, establish a target cost for every part in the new design.

Start the detailed design of the emerging product. Model, test, and evaluate the new design for form, fit, and function.

Reapply the process at the next logical point.

Share the results.

21.5 HIGHLY ACCELERATED STRESS SCREENING

Highly accelerated stress screening (HASS) is a proven test method developed to find manufacturing/production process–induced defects in electronics and electromechanical assemblies before those products are released to market. HASS is a powerful testing tool for improving product reliability, reducing warranty costs, and increasing customer satisfaction.

After a product has undergone Highly Accelerated Life Testing (HALT), HASS can be deployed in the production process. Once the product is made robust (through the application of HALT), the next logical step is to monitor the production processes using HASS. The goal of a HASS is to induce failure modes that can be inherent or introduced in the production process. HASS has been proven to be effective in screening failures that may have gone undetected in the burn-in testing process. A product that passes normal production tests but fails in a HASS would have probably failed early after product release, increasing warranty costs. HASS is used to improve the robustness/reliability of a product through test–fail–fix process where the applied stresses may be beyond the specified OLs determined by HALT. This is applied to 100% of the manufactured units.

There are two parts to HASS:

- HASS development/proof of screen (POS)
- HASS production screen

Since HASS levels are more aggressive than conventional screening tools, a POS procedure is used to establish the effectiveness in revealing production-induced defects. A POS is vital to determine that the HASS stresses are capable of revealing production defects but not so extreme as to remove significant life from the test item. Instituting HASS to screen the product is an excellent tool to maintain a high level of robustness, and it will reduce the test time required to screen a product resulting in long-term savings. Ongoing HASS screening assures that any weak components or manufacturing process degradations are quickly detected and corrected. HASS is not intended to be a rigid process that has an end point. It is a dynamic process that may need modification or adjustment over the life of the product. HASS testing benefits include the following:

- Assure manufacturing process and workmanship integrity
- Verify integrity of mechanical interconnects and component tolerance compatibility
- Identify and preclude escape of potential early life product failures

- Decrease product infant mortality and increase reliability
- Detect and correct design and process changes
- Detect and correct component variation
- Reduce production time and cost
- Increase out-of-box quality and field reliability
- Decrease field service and warranty costs
- Find manufacturing process problems
- Component placement (pick and place robotics)
- Solder and paste processes
- Integrated circuit (IC) vendor and/or process changes
- Detect margin shifts early
- Accelerate infant mortality failures
- Timing problems (that only occur under stress)
- Assembly errors—connectors, screws/fasteners
- Cable routing—rubbing, pinched solder connections

21.6 HIGHLY ACCELERATED STRESS AUDIT

Highly accelerated stress audit (HASA) is a proven test method developed to find manufacturing/production process–induced defects in electronics and electromechanical assemblies before those products are released to market. HASS can be applied to 100% of the manufactured units. HASA is an audit of the manufactured units and can be used where HASS has determined that the process has achieved statistical control.

There are 3 parts to HASA testing:

- HASS development/POS
- HASS production screen
- HASA production audit

Since HASS levels are more aggressive than conventional screening tools, a POS procedure is used to establish the effectiveness in revealing production-induced defects. A POS is vital to determine that the HASS stresses are capable of revealing production defects but not so extreme as to remove significant life from the test item. Instituting HASS to screen the product is an excellent tool to maintain a high level of robustness, and it will reduce the test time required to screen a product, resulting in long-term savings. Ongoing HASS screening assures that any weak components or manufacturing process degradations are quickly detected and corrected. HASS is not intended to be a rigid process that has an end point. It is a dynamic process that may need modification or adjustment over the life of the product. HASS aids in the detection of early life failures. HASA's primary purpose is to monitor manufacturing and prevent any defects from being introduced during the process. A carefully determined HASA sampling plan must be designed that will quickly signal when process quality has been degraded.

21.7 THE MANUFACTURING PROCESS

The process of producing new products may be said to be a multiphased process consisting of the following:

- Preproduction activity
- The pilot-run build
- The production run
- Delivery to the customer

21.7.1 Preproduction Activity

Prior to the first manufacturing build, manufacturing is responsible for completing a myriad of activities.

Manufacturing and engineering should work together to identify proposed technologies and to assure that the chosen technology is manufacturable.

The selection of suppliers should begin by consulting the current approved suppliers listing to determine if any of the existing suppliers can provide the technology and/or parts. A new supplier evaluation would be necessary if a supplier is being considered as a potential source for a component, subassembly, or device.

A pilot-run plan must be developed that specifies the quantity of units to be built during the pilot run, the yield expectations and contingency plans, the distribution of those units, the feedback mechanism for problems, the intended production location, staffing requirements, training plan, postproduction evaluation, and any other key issues specific to the project.

The manufacturing strategy needs to be developed. The strategy must be documented and communicated to appropriate personnel to ensure that it is complete, meets the business objectives, and ultimately is reflected in the design of the product. Developing a strategy for producing the product involves work on five major fronts:

- The production plan
- The quality plan
- The test plan
- The materials plan
- The supplier plan

The production plan details how manufacturing will produce the product. The first step is defining the requirements of the production process. Some of these requirements will be found in the business proposal and product specification. A bill of materials structure is developed for the product that best meets the defined requirements. Based on this bill of materials, a process flow diagram can be developed along with specific details of inventory levels and locations, test points, skills, resources, tooling required, and processing times.

The quality plan details the control through all phases of manufacture, procurement, packaging, storage, and shipment, which collectively assure that the product meets specifications. The plan should cover not only initial production but also how the plan will be matured over time, using data collected internally and from the field.

The test plan specifies the "how" of the quality plan. This document must have enough technical detail to assure that the features are incorporated in the product design specification. Care must be taken to ensure that the manufacturer's test strategies are consistent with those of all suppliers.

The materials plan consists of defining the operating plan by which the final product, parts, accessories, and service support parts will be managed logistically to meet the launch plans. This involves product structure, lead times, inventory management techniques, inventory phasing/impact estimates, and identification of any special materials considerations that must be addressed. Any production variants that will be in production as well as potentially obsolete products would be detailed.

The supplier plan consists of a matrix of potential suppliers versus evaluation criteria. The potential suppliers have been identified using preliminary functional component specifications. The evaluation criteria should include business stability, quality systems, cost, engineering capabilities, and test philosophy.

The DFMA review should be held when a representative model is available. This review should be documented, with action items assigned.

21.7.2 The Pilot-Run Build

The objective of this phase is to complete the pilot run and validate the manufacturing process against the objectives set forth in the manufacturing strategy and the product specification.

The pilot-run build is the first build of devices using the manufacturing documentation. It is during this phase that training of the assembly force takes place. All training should be documented so no employee is given a task without the appropriate training prior to the task.

The pilot-run build will validate the manufacturing process against the strategy and the manufacturing documentation. The validation will determine if manufacturing has met its objectives, including the following:

- Standard cost
- Product quality
- Documentation
- Tooling
- Training
- Process control

The validation will also determine if the production testing is sufficient to ensure that the product meets the specified requirements.

The pilot-run build also validates the supplier plan and supplier contracts. The validation will determine if the manufacturing plan is sufficient to control the internal processes of the supplier. The method and ground rules for communication between the two companies must be well defined to ensure that both parties keep each other informed of developments that impact the other. It should also confirm that all points have been addressed in the supplier contract and that all the controls and procedures required by the agreement are in place and operating correctly.

Internal failure analysis and corrective action take place, involving investigating to the root cause all failures during the pilot run. The information should be communicated to the project team in detail and in a timely manner. The project team determines the appropriate corrective action plans.

A pilot-run review meeting is held to review all aspects of the build, including the manufacturing documentation. All remaining issues must be resolved and documentation corrected. Sufficient time should be allowed in the project schedule for corrective action to be completed before the production run.

21.7.3 The Production Run

The objective of this phase is to produce high-quality product on time, while continuing to fine-tune the process using controls that have been put in place.

During this phase, the first production order of units and service parts are manufactured. The training effort continues, as new employees are transferred in or minor refinements are made to the process. Line failures at any point in the process should be thoroughly analyzed and the root cause determined. Product cost should be verified at this time.

21.7.4 Customer Delivery

The objective of this phase is to deliver the first production units to the customer, refine the manufacturing process based on lessons learned during the first build, and finally, monitor field unit performance to correct any problems.

Following production and shipment of product, continued surveillance of the production process should take place to measure its performance against the manufacturing strategy. The production process should be evaluated for effectiveness as well as unit field performance. Feedback from

the field on unit problems should be sent to the project team, where it may be disseminated to the proper area.

EXERCISES

1. Year 2000 (Y2k) problems were a concern for medical device manufacturers, especially those that dealt with imbedded microprocessors. Investigate this statement using a web search. How might the GMP regulation have avoided this problem?
2. Visit the website http://www.fda.gov/cdrh/dsma/gmp_man.html and briefly look at the manual listed here. How does this differ from the GMP regulation?
3. Perform a web search for DFMA; report on the best site you can find.
4. Find and report on at least one good example of DFA or DFMA.
5. A related term involves design for the environment. Find information on this type of process and report on its value.
6. A related activity involves design for life cycle; report on this concept.
7. Investigate a typical blood pressure unit that may be purchased at your corner drug store. What improvements can you suggest with respect to DFA?
8. As in exercise 7, but investigate an in-the-ear temperature unit.

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22 Miscellaneous Issues

When you get right down to it, one of the most important tasks of a leader is to eliminate his people's excuse for failure.

Robert Townsend

22.1 INTRODUCTION

There are several short topics that need to be a part of every designer's vocabulary and/or tool kit. This chapter will consist of several topics that will broaden the reader's expertise in several of these areas. These include such topics as learning from failure, design for *X*, product life issues, poka-yoke, and so forth.

22.2 LEARNING FROM FAILURE (AND LIES)

It is important to recognize that the engineering profession has learned from failures and the study of their causes. An exposure to such classical failures as the Tacoma Narrows Bridge, the Shuttle Challenger, the Hyatt Regency walkway collapse, Three Mile Island, the Bhopal Chemical Plant disaster, the World Trade Center disasters, and more recently, the collapse of the I35W Bridge in Minneapolis, amongst others, should be a part of every engineer's education (see, for example, http://www.matscieng.sunysb.edu/disaster/). Most disasters are the result of a combination of unexpected circumstances, poor design, and/or ethical failures, but not all.[1]

A brief mention of a number of biomedical engineering–related failures should help point out some of the considerations that students in bioengineering should consider in the process of design activities. Other examples are in various sections of this text to assist in a sensitization to the need for safe design procedures.

A computer programming glitch on a Therac-25 radiation therapy machine allowed a technician to deliver over 125 times the required therapeutic dose of radiation to a patient. The error message "Malfunction 54" did not convey the correct message that the technician should not repeat the dose. Needless to say, the patient died.[2]

Technicians in an ambulance taking a heart attack victim to a hospital lost use of their heart machine every time they attempted to use their radio transmitter. (The fault was caused by unshielded radio frequency interference.) The patient died.[3]

Toxic shock syndrome plagued some users of super absorbency tampons in the late 1970s. It also caused some deaths. There had been no Food and Drug Administration (FDA) or other guidelines as to the composition, degree of absorbency, or recommendations on length of use (time) for these products until this occurred.

Thalidomide was sold in Europe in the late 1950s, causing over 8000 births of malformed children. The drug had not been tested adequately prior to market release.

Laetrile, a substance that can be extracted from apricot seeds (or synthesized), has been touted as a cancer cure since the 1960s. Banned in the United States by the FDA, it can still be obtained in Mexico.

In 1938, 107 deaths of (primarily) children were caused due to ingestion of Elixir of Sulfanilamide, a toxic combination of diethylene glycol and sulfa. This one disaster is one of the prime initiators of the early FDA drug (especially patent drug) enforcement activities. Continued FDA monitoring of drugs via the FDA Adverse Event Reporting System (FAERS) is essential to monitor phase-four (sales) reactions to drugs. FAERS is a voluntary caregiver and/or user (and lawyer) reporting system used to track adverse drug events; available are databases of adverse drug events and various warning letters. FAERS is similar to Medical and User Device Experience (MAUDE), but is mainly for drug reactions, and is a part of the overall government drug/device monitoring system termed "MedWatch" (see http://www.fda.gov/Safety/MedWatch/default.htm for more information). Between the expected drug manufacturers' monitoring of drug events and the FDA monitoring of reported drug events, it is hoped that major adverse drug reactions may be caught early, rather than after many people are injured.

Quack medical devices have plagued the U.S. population for years. Most advertisers' claims for devices or drugs that have claims for medical benefits come under the scrutiny of the FDA, which has the power to fine manufacturers and force recalls as necessary. The website http://museumofquackery.com/covers many of the questionable medical devices of the past. Entrepreneurs, however, still exist that will and do make false claims for current quack medical devices, such as battery-operated (or manual) spark fire starters touted as pain relievers. Websites such as http://www.quackwatch.com/ and http://www.quackmedicine.com/ are worth reviewing when considering new drugs and/or devices.

22.3 DESIGN FOR *X*

There are a series of areas of design that are categorized as "design for *x*," where *x* is or involves some attribute of a portion of or all of the design (http://www.emdt.co.uk/article/design/design-for-x-and-be-prepared-for-anything). *X* can be, for example, usability, safety, manufacturability, calibration, assembly, maintenance, manufacture, production, aesthetics, disassembly, sterilization, recycling, and so forth. A few of those more relevant to bioengineering are covered here.

22.3.1 Design for Failure

It is important to consider, when designing systems and devices, that sometimes, you must consider and plan for failure. One must often be proactive, rather than reactive, when considering failure. Designing for failure can be for the purposes of safety and for convenience.

Safety considerations are paramount in many design problems, and an understanding of several examples is important. A few examples follow:

- Fuses—Current flow through a fine wire or a low-temperature-melt-point wire causes it to vaporize or melt, protecting the circuit beyond the fuse point.
- Shear pins—Many devices have a section that will break, rather than ruin the entire system. Many lawnmowers have a shear pin, which breaks before the main crankshaft can.
- Sprinkler systems—The increase in temperature due to a fire causes melting of a metal plug and the opening of a sprinkler or gas quenching system to put out the fire.
- The coating on a medicine "lasts long enough" in the stomach to deliver a drug to the intestines, where it is needed or causes no harm compared to direct stomach delivery (enteric coatings, a variation on the M&M "melts in your mouth, not in your hands" philosophy).
- Individually bubble-packed drugs stay isolated from the atmosphere (generally used with hydroscopic drugs) until the bubble is "burst."
- A humidification/heating system is allowed to operate until a bimetallic element snaps a vent shut at a given temperature (too hot or too cold).

- In the event of a power failure, a lead shield drops in front of a cobalt therapy delivery unit.
- A current limiter is placed between a patient and a medical device; the patient is protected from excessive currents.
- Bottle tops can be fashioned to require a minimal amount of squeezing and/or manipulation before they open, thus protecting the weak or young (typically for dispensing of medicines).
- Plastic or real peanuts are used for packing deform during impacts, protecting the packaged item.
- Graphite rods are designed to drop into nuclear reactors to quell runaway reactions.
- Feathers protect a bird but pull out in order to enable a bird to escape a predator.
- Eggshells protect an embryo but can be shattered from within by a chick ready to hatch.
- Pine seed can sit dormant for years, opening after a fire when there then exists a chance for sunlight and growth.

For systems such as computer security systems, the goal of a safe design would be to do the following: deter intrusion, detect intrusions, delay intrusions, warn of intrusions, and perhaps redirect intrusions to a "honeypot" system that can collect information on the intruder. Military systems can be designed so that in case of the failure of an outer system, an inner ring picks up on the challenge.

22.3.2 Design for Convenience

Many items are designed to fail in a particular manner only for the convenience of the user; a quick listing of a few of these items includes the following:

- Postage stamps—Sheets of postage stamps typically contain individual stamps separated by perforations. A slightly skilled user can easily separate out an individual stamp by causing failure along the perforations. Obviously, this same concept has been applied to toilet paper, paper towels, and checkbooks.
- Waffles in family and other packs typically are packed two or four to a sheet, the connections between the waffles being much thinner than any other part in order to allow ease of separations.
- Scoring of a surface to enhance breakage is a common way to ensure easily opened bags of coffee and pop-top cans of various designs.

22.3.3 Design for Assembly

The term *design for assembly* refers to a technique whereby the design and manufacturing considerations involved in an assembled device are optimized for ease of assembly of the device. Special attention is given to tolerances of parts that fit together, requirements for each part (in terms of motions to place the part in the assembly), and standardization of the assembly materials. Design-for-assembly methods are credited with major cost savings in several industries. An example would be the use of cotter pins rather than nuts and bolts in an assembly.

22.3.4 Design for the Environment

Another *design for* term potentially of interest is design for the environment. This term applies to the "clean" manufacturing and recycling of devices, including packaging. Devices are to be built using a minimum of energy, with minimum emissions and scrap and by-products. As much as is possible, packaging materials are also meant to be reused or recycled. End-of-life issues, such as recyclability and salvaging issues, also need to be considered.

22.3.5 Design for Developing Countries

The majority of the information in this text has not directly considered the special accommodations that must be made for developing medical device and process designs in any but first-world countries. This brief section of this chapter is aimed at giving the reader a brief overview of some of the special considerations that are a part of design or anticipated design projects involving biomedical engineering projects in developing countries. The overview is meant to be for the reader and for instructors using this text in order to facilitate such design projects.

The reader is encouraged to look at the following four main sources of information relevant to this task. These include the United Nations (UN) Millennium Development Goals, BIO Ventures for Global Health, the Gates Foundation Grand Challenges in Global Health, and other compendia of information as may be found on various university design websites and publications.

The UN has officially published eight poverty-related goals. These may be found online at the website http://www.un.org.millenniumgoals. Millennium goal one is relevant in that it sets as a call decreasing extreme poverty and hunger. Included in the descriptors for this call is the fact that the international poverty line is designated as wages of less than $1.25 per day in year 2005 prices. In 2005, 1.4 billion people fell below this figure. The reader should immediately infer that design for the developing world is extremely cost sensitive.

Millennium development goal number four calls for reduction of child mortality. The under-age-5 mortality rate was 72 deaths per thousand live births in 2008. Millennium goal five is aimed at improving maternal health. In developing regions, maternal mortality is still around 450 per 100,000 live births in 2005. Goal six involves combating HIV/AIDS, malaria, and other diseases. Design projects involving rapid testing for diseases, improvement of childbirth education and assistance, and development and dissemination of lower-cost antibiotics and antivirals are all needed.

Millennium goal seven involves environmental sustainability. Without safe water and sanitation and sanitary practices, about one-fourth of the world's population is at risk. Design projects involving improvements of water quality and improvements in disposal of waste products are desperately needed.

The company BIO Ventures for Global Health (http://www.bvgh.org/Biopharmaceutical-Solutions/Data-Center/BVGH-Reports.aspx) has a number of publications relevant to design of diagnostics for the developing world. Of special interest is the publication "The Diagnostics Innovation Map, Medical Diagnostics for the Developing World" (http://www.bvgh.org/LinkClick.aspx?fileticket=-a1C6u2LE4w%3d&tabid=91). This publication has excellent elaboration on many of the real constraints of "minimal infrastructure" (also known as developing world) environments for diagnostics applications, such as the following:

1. Cost (as low as possible, under $2 per test)
2. Power (none if possible, batteries or solar if possible)
3. Water (prefer none, otherwise, may need to provide)
4. Refrigeration (not likely)
5. Stability (design for high and low temperatures, high humidity)
6. Training (assume minimal or none)
7. Human interface (intuitive, language independent)
8. Rapid test to result

Appendix information is included for the researcher interested in unmet diagnostic needs for specific diseases.

The Gates Foundation (http://www.grandchallenges.org/Pages/BrouseByGoal.aspx) has asked for grant proposals in the following 16 areas:

1. Create effective single dose vaccines that can be used soon after birth
2. Prepare vaccines that do not require refrigeration
3. Develop needle-free delivery systems
4. Devise reliable tests in model systems to evaluate live attenuated vaccines
5. Solve how to design antigens for effective, protective immunity
6. Learn which immunological responses provide protective immunity
7. Develop a biological strategy to deplete or incapacitate a disease-transmitting insect population
8. Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population
9. Create a full range of optimal, bioavailable nutrients in a single staple plant species
10. Discover drugs and delivery systems that minimize the likelihood of drug resistant microorganisms
11. Create therapies that can cure latent infection
12. Create immunological methods that can cure chronic infections
13. Develop technologies that permit quantitative assessment of population health status
14. Develop technologies that allow assessment of multiple conditions and pathogens at point of care
15. Discover biomarkers of health and disease
16. Discover new ways to achieve healthy birth, growth, and development

A review of each of these challenges is recommended for the reader. It should be apparent that all are in concert with the aforementioned UN millennium goals.

There are a number of universities that sponsor multiple international biomedical engineering–related student design projects. A partial list follows; a visit to some of the related websites is recommended.

Rice University has a program titled "Beyond Traditional Borders (BTBs)," which involves an undergraduate program in global health technologies. Students in BTB work in interdisciplinary teams to design low-cost technologies that address challenges to health care delivery identified by clinicians in the developing world. Exceptional students undertake international internships to implement their technologies under the guidance of physicians and nurses in clinics and hospitals in the developing world (http://www.rice360.rice.edu/tech).

The University of Michigan has developed a graduate-level course titled "Design for Global Health: Sustainable Technology for the Developing World," which has resulted in several student projects and the development of an open-access compendium of medical devices designed to be implemented in the developing world (http://www.appropedia.org/Portal:Medical_Devices). This portal is a useful first stop when looking at development of new technologies, and will be added to. The course outline[4] is useful for those planning such a course.

Duke University has a program titled "Engineering World Health," which involves unique study-abroad programs for study and work in developing-world health care settings (http://www.ewh.org/). Projects have typically been posted annually that may be undertaken by interested students in the United States and elsewhere.

Northwestern University has a program titled "Center for Health Care Technologies." Undergraduate engineering majors interested in global health may apply to enroll in the Global Health Technologies (GHTs) program. On-site work and supervision in the townships of Cape Town, South Africa provides students with hands-on experience in developing and managing technology infrastructure to improve health outcomes in resource-poor environments (http://www.cight.northwestern.edu/education/study_abroad.html).

This is but a partial listing of programs available and is not meant to be comprehensive. Possibilities likely exist wherever you are for work in developing countries or even in your own area's needier spots.

To summarize, design for the developing world involves all the topics elsewhere in this text. The differences lie mainly in that some design constraints are taken to the extreme (lowest possible cost,

highest reliability, for example) and that some are not design topics but questions of access to the populations to be served.

22.3.6 Design to Combat Customer Misuse

Designs must be able to ensure that misuse of a device by the user will not cause the device to fail or operate out of specification. The designer must consider the types of misuse that may occur and design to prevent failure. Some examples of misuse include the following:

- Dropping a device
- Misconnecting a device
- Adding incorrect information to a software program
- Pressing the wrong key on a keyboard or display
- Inserting a battery in the reverse position
- Operating the device without reading the manual

An example from industry is a doctor who was going to change the battery in a device for neural stimulation. The device was operated by a 9V battery. The design was such that the battery could be placed in the device in only one way. The doctor decided he wanted to place it in backward. When he could not do it by hand, he used a hammer. Then he called the company and complained his device did not work. Design engineers should do their best to reduce the effect of customer misuse, but they cannot make it idiot-proof.

A manufacturer made a device for delivering anesthesia during surgery. They made a table, attached to the machine, where the anesthesiologist could make notes or place anesthetic agents. Unfortunately, they did not anticipate that during lulls in activity, the anesthesiologists would sit on the table part. After several complaints of bent tables, the manufacturer added extra support to the table to support typical anesthesiologists.

Finally, a highly software-driven anesthesia machine was delivered to a hospital. The operating manual was handed to the chief surgeon. He refused to accept it, saying his undergraduate degree was in electrical engineering, and being an engineer, he intuitively knew how to operate the device. Within 24 hours, he was on the phone asking how the machine worked. Beware of doctors with engineering undergraduate credentials.

22.3.7 Design for Manufacturability

Design for manufacturability ensures that a design can be repeatedly manufactured while satisfying the requirements for quality, reliability, performance, availability, and price. One fundamental principle is reducing the number of parts in the device. Existing parts should be simple and add value to the product. All parts should be specified, designed, and manufactured to allow 100% usable parts to be produced. Design for manufacturability is desirable because it reduces cost, due to the following:

- A simpler design with fewer parts
- Simple production processes
- Higher quality and reliability
- Easier to service

22.3.8 Design for Serviceability

Design for serviceability ensures that a design can be repeatedly serviced, without undue labor, to maintain optimum performance. Reduction in parts helps to achieve this goal. Placement of

components in a device is also important. Those components that will need to be replaced on a periodic basis should be placed near the outside of the device to ensure easy access. PC boards should be easy to replace. Connections should be marked or have some means of preventing misconnections when the device is reassembled. An example would be two similar cables in the same area of the device. There must be some means to indicate which cable goes in which connection.

22.4 UNIVERSAL DESIGN

The term *universal design* (sometimes called *design for all*) refers to a mind-set that is inclusive in nature when one is considering the design of new environments and products.[5] Briefly, it gives special consideration to design elements that may be altered to include persons with abilities not falling within the "norm" (including the elderly), without calling special attention to the fact that such a design change has been made. These abilities are inclusive and might include problems including hearing, vision, balance, strength, attention, memory, and so forth. A reminder system for pill dispensing for the elderly thus might have a louder-than-normal alarm and visual indicators to indicate that a drug has not been taken. Wider-than-normal doors, for example, is a case of universal design (to allow ease of wheelchair entry). Cut curbs are another example.

It must be noted that the (U.S.) Americans with Disabilities Act (ADA) preceded this endeavor label. The ADA prohibits discrimination and ensures equal opportunity for persons with disabilities in employment, state and local government services, public accommodations, commercial facilities, and transportation. It also mandates the establishment of telecommunications devices for the deaf (TDDs)/telephone relay services. There are a number of published ADA standards for accessible design that have been codified in our legal system (see, for example, 28CFR Part 36, ADA Standards for Accessible Design).

The basic premises used in universal design are as follows: equitable use, flexibility in use, simple/intuitive, ergonomic in terms of feedback, error-forgiving, physically easy to use, and appropriateness of size and usability.

The reader is referred to the ADA website (http://www.ada.gov/) for up-to-date legislation and design information. The reader is referred to the website http://www.universaldesign.com/ for up-to-date continuing education and other learning possibilities. For a listing of texts in the area, see http://www.universaldesignresource.com/information/view/9.

22.5 PREVENTION THROUGH DESIGN

A meeting was held in 2007, sponsored by the National Institute of Safety and Health (NIOSH), on the topic of "Prevention through Design." The premise of the meeting/workshop was that many accidents are due to faulty design at the outset and that design techniques need to be developed that consider prevention of potential future accidents. The audience for this workshop consisted of personnel from a multitude of industries, from mining to health care. One of the major questions addressed by some of the speakers was the necessity to prove to management that money spent at the outset for improved safety paid for itself many times over in long-term costs of doing business. This group's efforts will likely bring new legislation to bear with respect to design education. Current information on this initiative may be found at http://www.cdc.gov/niosh/topics/ptd/.

22.6 *POKA-YOKE*

Poka-yoke is the name given to a methodology to fool-proof a process. It was developed as a part of the Toyota production system. Generally speaking, one of three types of techniques is used: a contact method (has contact been made properly?), a fixed-value method (have the proper movements been made?), a or motion-step method (have the prescribed steps been done in the correct order?). The use of the method involves studying the process that needs to be improved and then

deciding how to mistake-proof the process. This mistake-proofing step can involve prevention of an error being made (machine will not work without the part that needs to be added, or a part can only be fitted on one way); warning the worker involved that an error has been made; or a more serious flagging of the situation (audible alarm, for example).

22.7 PRODUCT LIFE ISSUES

The goal of the product development process is to put a safe, effective, and reliable medical device in the hands of a physician or other medical personnel where it may be used to improve health care. The device has been designed and manufactured to be safe, effective, and reliable. The manufacturer warranties the device for a certain period of time, usually 1 year. Is this the end of the manufacturer's concern about the device? It should not be. There is too much valuable information to be obtained.

Analysis of field data is a means of determining how a product is performing in actual use. It is a means of determining the reliability growth over time. It is a measure of how well the product was specified, designed, and manufactured. It is a source of information on the effectiveness of the shipping configuration. It is also a source for information for product enhancements or new designs. Field information may be obtained in any of several ways, including the following:

- Analysis of field service reports (FSRs)
- Failure analysis of failed units
- Warranty analysis

22.7.1 Analysis of Field Service Reports

The type of data necessary for a meaningful analysis of product reliability are gathered from FSRs. The reports contain such vital information as the following:

- Type of product
- Serial number
- Date of service activity
- Symptom of the problem
- Diagnosis
- List of parts replaced
- Labor hours required
- Service representative

The type of product allows classification by individual model. The serial number allows a history of each individual unit to be established and traceability to the manufacturing date. The date of service activity helps to indicate the length of time until the problem occurred.

The symptom is the problem, as recognized by the user. The diagnosis is the description of the cause of the problem from analysis by the service representative. The two may be mutually exclusive, as the cause of the problem may be remote from the user's original complaint. The list of parts replaced is an adjunct to the diagnosis and can serve to show trends of parts usage and possible vendor problems. The diagnosis is then coded, from which it may later be sorted.

The required labor hours help in evaluating the complexity of a problem, as represented by the time involved in repair. They, along with the name of the service representative, act as a check on the efficiency of the individual representative, as average labor hours for the same failure code may be compared on a representative-to-representative basis. The labor hours per problem may be calculated to assist in determining warranty cost as well as determining the efficiency of service methods.

The only additional data that are not included in the FSR are the date of manufacture of each unit and the length of time since manufacture that the problem occurred. The manufacturing date is kept on file in the device history record. The length of time since manufacture is calculated by subtracting the manufacturing date from the date of service.

22.7.1.1 The Database

FSRs are sorted by product upon receipt. The report is scanned for completeness. Service representatives may be contacted where clarification of an entry or lack of information would lead to an incomplete database record. The diagnoses are coded, according to a list of failures, as developed by reliability assurance, design engineering, and manufacturing engineering (Table 22.1). Manufacturing date and the length of time since manufacture are obtained. The data are then ready to be entered into the computer.

The data are entered into a computer database, where they may be manipulated to determine the necessary parameters. Each FSR is input to a single database record, unless the service report contains multiple failure codes. Figure 22.1 shows a sample database record.

The data are first sorted by service date, so trending can be accomplished by a predetermined time period, such as a fiscal quarter. Data within that time frame are then sorted by problem code, indicating the frequency of problems during the particular reporting period. A Pareto analysis of the problems can then be developed. Data are finally sorted by serial number, which gives an indication of which devices experienced multiple service calls and/or experienced continuing problems.

Percentages of total problems are helpful in determining primary failures. Spreadsheets are developed listing the problems versus manufacturing dates and the problems versus time since manufacturing. The spreadsheet data can then be plotted and analyzed.

22.7.1.2 Data Analysis

The most important reason for collecting the field data is to extract the most significant problem information and put it in such a form that the cause of product problems may be highlighted, trended, and focused upon. The cause of the problem must be determined and the most appropriate solution implemented. A Band-Aid solution is unacceptable. Company response to problems involving any problem worthy of reporting in the FDA MAUDE database is critical. Companies must show that

TABLE 22.1
List of Failure Codes

Failure Code	Failure
Base machine	
101	Missing parts
102	Shipping damage
103	Circuit breaker wiring damage
104	Regulator defect
105	Shelf latch broken
Monitor	
201	Display problems
202	Control cable defect
203	Power board problem
204	Control board problem
205	Unstable reference voltage

Source: From Fries, R. C., *Reliable Design of Medical Devices*, Marcel Dekker, Inc., New York, 1997.

Field	Field content
1	Service date
2	Device serial number
3	Manufacturing date
4	Time in use (hours)
5	Failure code
6	Failed parts 1
7	Failed parts 2
8	Failed parts 3
9	Failed parts 4
10	Failed parts 5
11	Time to repair (hours)
12	Service representative ID

FIGURE 22.1 Sample database record. (From Fries, R. C., *Reliable Design of Medical Devices*, Marcel Dekker, Inc., New York, 1997.)

they are responsive to user complaints and have a process in place for complaint correction. The use of a consistent response to user complaints, such as "user error," is not a legally defensible position.

Pareto analysis is used to determine what the major problems are. The individual problems are plotted along the *x*-axis and the frequency on the *y*-axis. The result is a histogram of problems, where the severity of the problem is indicated, leading to the establishment of priorities in addressing solutions. Similar plots versus day of week may indicate personnel problems, versus supplier may indicate supply problems.

Several graphical plots are helpful in analyzing problems. One is the plot of particular problems versus length of time since manufacturing (sometimes termed a "run plot"). This plot is used to determine the area of the life cycle in which the problem occurs. Peaks of problem activity indicate infant mortality, useful life, or wear-out, depending on the length of time since manufacture. An example plot may be seen in Figure 22.2; the data are taken from a complaint investigation done in 2007. One may surmise that the units are in the "infant mortality" stage of their life, as the complaint rate has not yet risen after 6 years. This is an interesting case, as the "guarantee" on the unit is only 1 year.

A second plot of interest is that of a particular problem versus the date of manufacture. This plot is a good indication of the efficiency of the manufacturing process. It shows times where problems occur, for example, the rush to ship product at the end of a fiscal quarter, lot problems on components, or vendor problems. The extent of the problem is an indication of the correct or incorrect solution. An example of this type of data may be seen in Figure 22.3. One may infer from the plot that complaints start immediately after manufacture and distribution (infant mortality) and continue throughout the life of the devices. Vertical gaps are indicative of product recalls (2005 and 2006). A general lightening of complaints from left to right may be indicative of improved maintenance or withdrawal of old product from the market.

Another useful plot is that of the total number of problems versus the date of manufacture. The learning curve for the product is visible at the peaks of the curve. It can also be shown how the

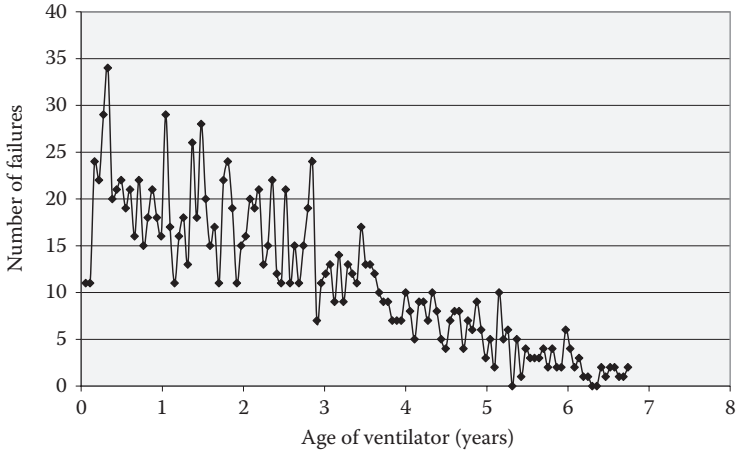

FIGURE 22.2 MAUDE complaints versus age of ventilator.

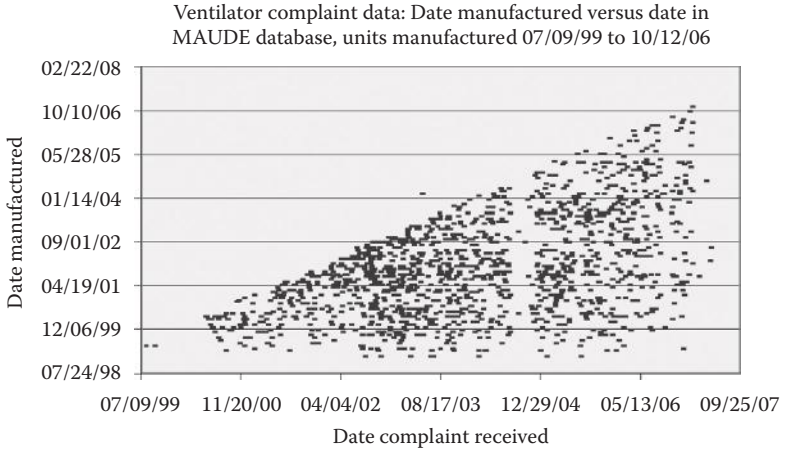

FIGURE 22.3 This plot contains complaint data versus manufacturing date (same ventilators).

problems for subsequent builds decrease as manufacturing personnel become more familiar and efficient with the process.

Trending of problems, set against the time of reporting, is an indicator of the extent of a problem and how effective the correction is. Decreasing numbers indicate that the solution is effective. Reappearing high counts indicate that the initial solution did not address the cause of the problem.

The database is also useful for analyzing warranty costs. The data can be used to calculate warranty expenses, problems per manufactured unit, and warranty costs as a percentage of sales. A similar table can be established for installation of devices.

22.7.2 Failure Analysis of Field Units

Most failure analysis performed in the field is done at the board level. Service representatives usually solve problems by board swapping, since they are not equipped to troubleshoot at the component level. Boards should be returned to be analyzed to the component level. This not only yields

TABLE 22.2
Warranty Analysis

Product Code	Parameters	Cost 1/95	Cost 2/95	Cost Year to Date
xxxxx	Normal warranty	$	$	$
xxxxx	Recall warranty	$	$	$
xxxxx	Total warranty	$	$	$
xxxxx	Setup cost	$	$	$
xxxxx	Total cost	$	$	$
xxxxx	Sales	$	$	$
	Warranty/sales			
	Setup/sales			
	Total/sales			
	Number of units shipped			
	Number of units setup			
	Number warranty units			
	Number of recall units			
xxxxx	Warranty/unit	$	$	$
xxxxx	Recall/unit	$	$	$
xxxxx	Setup/unit	$	$	$
xxxxx	Total/unit	$	$	$

Source: From Fries, R. C., *Reliable Design of Medical Devices*, Marcel Dekker, Inc., New York, 1997.

data for trending purposes but also highlights the real cause of the problem. It also gives data on problem parts or problem vendors.

The most important process in performing field failure analysis is focusing on the cause of the problem, based on the symptom. It does no good to develop a fix for a symptom if the cause is not known. To do so only creates additional problems. Analysis techniques, such as fault tree analysis or failure modes and effects analysis (FMEA), may help to focus on the cause.

Once the component-level analysis is completed, Pareto charts may be made, highlighting problem areas and prioritizing problem solutions. The major problems can be placed in a spreadsheet and monitored over time. Graphical plots can also be constructed to monitor various parameters over time.

22.7.3 Warranty Analysis

Warranty analysis is an indication of the reliability of a device in its early life, usually the first year. Warranty analysis (Table 22.2) is a valuable source of information on such parameters as warranty cost as a percentage of sales, warranty cost per unit, installation cost per unit, and percentage of shipped units experiencing problems. By plotting these data, a trend can be established over time.

22.8 PRODUCT TESTING ISSUES

Analysis of field data is also a significant means of reviewing the testing completed during the product development cycle to determine if it was sufficient for the intended use of the device. If field reports indicate a litany of problems, the types and severity of the testing performed need to be reviewed. Highly Accelerated Life Testing (HALT) may have needed to be performed, as this type of testing may indicate problems early in the testing that would take some time to occur in the field. The severity of the test parameters needs to be reviewed to determine if more severe parameters

could have indicated a problem was present. If the failure was caused by customer misuse of the product, the type and severity of the misuse testing needs to be reviewed.

When reviewing the tests that were performed, it is important to analyze test severity, as you want the test parameters to be severe enough to indicate a weakness in the design or component, yet you do not want the parameters so severe that they cause problems that would not occur under ordinary use of the device.

EXERCISES

1. Find and report on heart valve failure history. What valves and valve types are still in the development phase?
2. Find information on the health effects of the Chernobyl accident; report on the current state of this event.
3. Your Volvo hits a guardrail at high speed. How many systems are involved in the incident as a design-to-fail device? Detail these (at least three).
4. There was a significant social outcry associated with the lack of patient informed consent in a long-term study of syphilis in the U.S. South in the 1900s. Find and discuss information on this event.
5. Illegal medical experimentation was detected during World War 2. Find information on this and report on the outcomes.
6. There are a few excellent websites dealing with ethical issues in the United States. Find one and document what is at the site.
7. Find and discuss at least one good university website relating to medical ethics.
8. Find and report on the Bhopal incident. What elementary safety rule was violated in this case?
9. Find and discuss at least one new design-for-failure example.
10. Find and discuss at least one design-for-convenience example.
11. Find and discuss material relating to Universal Design for Learning.

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23 Professional Issues

> A man's ethical behavior should be based effectually on sympathy, education, and social ties; no religious basis is necessary. Man would indeed be in a poor way if he had to be restrained by fear of punishment and hope of reward after death.
>
> **Albert Einstein**

This chapter will discuss several professional issues relating to professionalism in biomedical engineering (BME). Specifically, it will cover some of the alphabet soup of professional societies that many biomedical engineers are members of and/or need to be familiar with as they are also standards-setting groups. Next, it will cover licensing of engineers and the ramifications for practicing biomedical engineers, especially those working in the area of forensics. Lastly, it will briefly discuss issues relating to continuing education for both licensed and unlicensed engineers.

23.1 BME-RELATED PROFESSIONAL SOCIETIES

Society memberships, properly chosen, can be an invaluable aid in professional pursuits. Memberships should allow for one to meet others with related professional interests, assist in professional advancement through relevant newsletters and professional magazines, and share knowledge and acquire new knowledge through regularly scheduled reasonably convenient national meetings. These meetings, and any related social events, should allow one to "network" with others for potential collaborations. Most societies will also have a web presence and a means for distribution of job opportunities. The results of these meetings should be archived and be a part of the membership benefits of the organization. Some of the groups also provide standards-setting functions; the ability to sit on such committees can be a useful experience.

23.1.1 BME Societies

Many campuses have a small number of societies that relate directly to BME; the choice of societies can widen dramatically upon graduation and a first or later job. Some of the major societies relevant to various career paths in bioengineering are as follows:

1. AAMI—The Association for the Advancement of Medical Instrumentation is aimed at designers, managers, users, and regulators of medical technologies. As such, it is heavily hospital user and medical industry oriented, with a large clinical engineering emphasis. For medical product and process design engineers, it is a comprehensive and useful organization in which to be a member. For engineers working in a clinical or clinical research environment, membership is highly recommended. See http://www.aami.org for more information.
2. ACM—The Association for Computing Machinery has a special interest group: SIGBioinformatics, which emphasizes medical informatics and other topics such as multimedia and molecular databases. This group sponsors several workshops and conferences each year. (See http://www.acm.org; search for SIGBioinformatics.)

3. AMIA—The American Medical Informatics Association is a society devoted "to developing and using information technologies to improve health care" and is composed of individual, institutional, and corporate members. This group holds one major and one minor congress each year devoted to the application of informatics to problems in heath care, and collaborates with the International Medical Informatics Association (IMIA). Areas of endeavor include translational bioinformatics, clinical research informatics, clinical informatics, public health informatics, and medical informatics and medicine. For students considering informatics as a career, this society has a lot to offer. (See http://www.amia.org and http://www.imia.org for additional information.)
4. BMES—The Biomedical Engineering Society aims to "promote the increase of biomedical engineering knowledge and its utilization." This group is heavily academic (students to professors) oriented and provides one national meeting, one special interest group meeting (Cellular and Molecular Bioengineering), one newsletter, and three publications: *Annals of Biomedical Engineering*, *Cellular and Biomolecular Engineering*, and *Cardiovascular Engineering and Technology*. Many campuses have a student chapter. A major concern of the society is that it provides personnel from industry and academia to accreditation of bioengineering and BME programs. See http://www.bmes.org for additional information.
5. IBE—The Institute of Biological Engineering society aims to encourage interest and promote inquiry into biological engineering in its broadest manner, with potential application to the improvement of the human condition. This group is very broad in nature and includes many participants from agricultural engineering. Many of their yearly conferences are held in conduction with other groups that have some overlap in interests, such as the BMES. See http://www.ibe.org for additional information.
6. IEEE-EMBS—The Institute of Electrical and Electronics Engineers is a multinational society that represents many working in the electronics and related industries; one of its 38 societies is the Engineering in Medicine and Biology Society (EMBS). The membership in this group exceeds 9000, with about 25% of this membership outside the United States (97 countries). The group publishes or copublishes *Transactions on Biomedical Engineering*, *Transactions on Nanoscience*, *Transactions on Medical Imaging*, *Transactions on Neural Systems and Rehabilitation Engineering*, *Transactions on Computational Biology and Informatics*, *IEEE Reviews on Biomedical Engineering*, *IEEE Journal of Translational Engineering in Health and Medicine*, *Transactions on Biomedical Circuits and Systems,* as well as a bi-monthly magazine, the *IEEE-EMBS Magazine Pulse*. This society also sponsors one international conference each year. This full-service group represents the largest number of biomedical engineers of any organization. (See http://www.ieee.org; search for the EMBS group.)
7. RESNA—The Rehabilitation Engineering and Assistive Technology Society of North America "is an interdisciplinary association of people with a common interest in technology and disability." As might be expected from the title, this group is composed of a broad range of professionals interested in various aspects of assistive care and technology. This group holds an annual meeting; selected student design teams are invited to compete at the meeting. (See http://www.resna.org.)
8. SPIE—The Society of Photo-Optical Instrumentation Engineers is an international society specializing in photo-optical systems, many of which have biomedical applications. With a base of over 225,600 constituents from approximately 150 countries, the society advances emerging technologies through interdisciplinary information exchange, continuing education, publications, patent precedent, and career and professional growth. SPIE annually organizes and sponsors approximately 25 major technical forums, exhibitions, and education programs in North America, Europe, Asia, and the South Pacific. (See http://www.spie.org.)

9. The Society for Biomaterials promotes advances in biomedical materials research and development by encouragement of cooperative research, education programs, clinical applications, and professional standards in the biomaterials field. The group holds one annual meeting and publishes two major journals in the field. (See http://www.biomaterials.org.)
10. The American Society for Quality, formed after World War 2, now has members in over 140 countries. Its mission is to "increase the use and impact of quality in response to the diverse needs of the world." As you might imply from material in this text, this society has direct relevance to health care improvement as well. (See http://www.asq.org.)
11. The American Society for Artificial Internal Organs is composed of researchers and entrepreneurs involved in the field of artificial internal organs (kidney, heart, lung, etc.). It holds an annual conference, publishes one journal, and has recently involved student members. (See http://www.asaio.org for more information.)

Several of the major classical discipline-oriented groups have focus groups relating to BME. The American Society for Mechanical Engineers has a bioengineering division as one of its many subdivisions; this group holds a small conference each year. Most biomed-related papers are part of the yearly American Society of Mechanical Engineers (ASME) meeting; a small number are published at the bioengineering meeting. (See http://divisions.asme.org/BED/.) The American Institute of Chemical Engineering has a Food, Pharmaceutical and Bioengineering Division (FP&BE). The FP&BE division provides engineers and scientists interested in the field of food, pharmaceuticals, and bioengineering with places to join and to discuss. It also supplies technical publications and information in these fields, including papers at national institute meetings. With shifting emphases at various universities' ChE programs (Vanderbilt's ChE program, for example, has been renamed "Chemical and Biomolecular Engineering") this area will likely grow in impact. The American Society for Engineering Education sponsors a BME division as well as a Biological and Agricultural Division; these groups sponsor a number of sessions at the yearly conferences, some of which are joint offerings. (See http://www.asee.org/member-resources/groups/divisions.)

23.2 STANDARDS-SETTING GROUPS

In order to establish minimal standards for biomedical devices and some processes, many groups have established written standards in areas involving their expertise. These standards are then typically available for purchase; documentation that standards have been met then becomes a part of the continuing certification that a process or product meets specifications.

In the United States, standards setting is done by a mixture of professional societies, nongovernmental agencies, and governmental agencies. For example, AAMI sets standards in the areas of biomedical equipment, dialysis equipment, and sterilization. The American National Standards Institute (ANSI, http://www.ansi.org), an independent organization, coordinates U.S. voluntary standards and is the U.S. representative to the International Organization for Standardization (ISO). ANSI has a small number of standards that are uniquely theirs; they co-list with many of the other standards as being in agreement with those standards. The major governmental organization involved in standards is the Occupational Safety and Health Organization (OSHA); the majority of the standards here relate to health and safety of workers in the workplace. Specific standards apply to the health industry. A partial listing of U.S. standards-setting agencies and groups may be seen in Table 23.1.

Many nations have the majority of their standards-setting functions imbedded in a governmental-sponsored standards body. For a partial listing of such sites and representative standards, a good starting point is the publication *The Guide to Biomedical Standards* (Aspen Publishers, Inc., Gaithersburg, MD, ISBN 0-8342-1692-2, 1999).

TABLE 23.1
Representative U.S. Standards-Setting Organizations

Agency	Website
American Heart Association	http://www.aha.org
American Dental Association	http://www.ada.org
American Medical Association	http://www.ama-assn.org
American Society for Quality Control	http://www.asqc.org
American Society for Testing of Materials	http://www.astm.org
American Society of Mechanical Engineers	http://www.asme.org
Association for the Advancement of Medical Instrumentation	http://www.aami.org
Federal Communications Commission	http://www.fcc.gov
Institute of Electrical and Electronic Engineers	http://www.ieee.org
Joint Commission on Accreditation of Healthcare Organizations	http://www.jcaho.org
National Council on Radiation Protection and Measurements	http://www.ncrp.com
National Electrical Manufacturers Association	http://www.nema.org
National Fire Protection Association	http://www.nfpa.org
National Safety Council	http://www.nsc.org
Occupational Safety and Health Administration	http://www.osha.gov
Underwriters Laboratory	http://www.ul.com

The most influential international standards organization is the ISO (http://www.iso.org/iso/home.html), which is a worldwide federation of approximately 3000 national standards bodies from some 164 countries, one from each country (ANSI in the United States). The mission of the ISO is the development of consensus standards in order to facilitate the international exchange of goods and services, and the development of cooperation in the spheres of intellectual, scientific, technological, and economic activity. The ISO's work results in international agreements that are published as international standards. If successful, these standards will supplant the potentially 1164 or more individual country standards as time progresses.

23.3 PROFESSIONAL ENGINEERING LICENSURE

An extremely important decision in an engineer's career is that of applying for professional licensure. All states in the United States have statutes that establish the registration requirements for architects, engineers, landscape architects, and interior designers, and describe the size and scope of projects for which a registrant is needed. To improve the level of professional conduct and to establish a standard of care, the licensing board also enacts rules of professional conduct. A typical state licensure board holds its purpose to be one of safeguarding life, health, and property, and the promotion of the public welfare through the establishment of standards and regulating the practice of engineering within the state. It does this through general requirements regarding educational attainment, participation in practice, examination and licensure, continuing education requirements, and the publication and enforcement of codes of conduct for the practice of engineering.

The implications of licensure are increased earnings, better employment possibilities, a legal status for private practice opportunities such as consulting and expert witnessing, the ability to bid on government contracts requiring licensure, and the ability to offer your services to the public as a professional engineer (PE). According to the National Council of Examiners for Engineering and Surveying (NCEES), licensed engineers enjoy salaries 15% to 25% higher than nonlicensed engineers. Many state regulations specify the conditions under which a licensed engineer must

be supervisory; certain projects cannot be undertaken without this supervision, which includes certification with a signature and stamp. If called upon to testify in court regarding areas of your expertise, for example, a medical device accident investigation, the PE license and your experience as evidenced by your vita is generally enough to convince a judge that you are a credible witness. Professional licensure is a two-step process involving an engineering internship and examination and registration as a PE.

23.3.1 Engineering Internship

To become an engineering intern (also known as an engineer-in-training), the following conditions must (typically) be satisfied: (1) graduation (or a senior in good standing) from a minimum 4-year undergraduate engineering curriculum accredited by ABET (once the Accreditation Board for Engineering and Technology) or having an undergraduate degree determined to be substantially equivalent to an ABET-accredited degree, and (2) passage of the fundamentals of engineering examination (a full-day general comprehensive exam, passage is set at 70%). The NCEES passed a recommendation that the minimum educational level for the intern exam be raised to the equivalent of an MS in 2006 (to become mandatory by 2020), but as of this writing, no state has adopted this change. The exam is generally given twice a year. It is generated by the National Council of Examiners for Engineering and Surveying and administered by state-delegated examiners. (See http://www.ncees.org/exams for additional information.)

Fees for the exam are reasonable (~$50). Pass rates vary by state, dependent in part on whether or not the exam is mandatory for graduation from college. A pass rate of 60% or better is not uncommon. For many states, once this barrier is passed, the exam does not need to be retaken.

23.4 REGISTRATION AS A PROFESSIONAL ENGINEER

The following requirements must typically be satisfied for PE licensure:

1. Graduation from a minimum 4-year undergraduate engineering curriculum (or equivalent, as aforementioned) accredited by ABET (or substantial equivalency)
2. Four years of progressive engineering experience satisfactory to the board (often certified via plans developed, etc.)
3. Certification as an engineer intern or 12 years of progressive engineering experience satisfactory to the board
4. Passage of the Principles and Practice of Engineering examination in 1 of the 18 areas tested (mechanical, electrical, etc., a major day-long exam)

Item 3 may take the form of an oral examination and the documentation of experience as an engineering intern. Fees for this exam are reasonable. Pass rates vary considerably by state and by discipline. Tennessee, for example, had an overall pass rate just above 50% in 2006. Licenses are state dependent; thus, you must make application to practice as a practicing engineer in another state and pay any relevant license and “privilege” fees.

Once a person has passed the aforementioned registration process, the license must be maintained by the following:

1. Yearly license renewal fee payment
2. Yearly or other privilege tax payment (if mandated)
3. Proof of continuing education efforts (if requested)
4. Abiding by the rules of conduct as set forward by the state

23.5 RULES OF PROFESSIONAL CONDUCT

The following are general guidelines regarding the rules of professional conduct for the practice of engineering (National Society for Professional Engineers [NSPE]):

1. The registrant must recognize that the welfare of the public is paramount. If it is felt that the decisions made by one's employer (or client, etc.) are counter to this, it is the registrant's responsibility to report the decision to the appropriate authorities and to refuse to carry out the decision.
2. The registrant must perform service only in areas of personal competence. This service will typically be noted by the affixing of his/her signature and seal to documents prepared in this way. The affixing of this seal or signature to other documents can lead to dismissal and/or fines. Similar punishments will ensue due to violation of any regulations and acts of incompetence due to malpractice or disability.
3. Professional reports and expert testimony made by the registrant must be objective and truthful. If the registrant is speaking on behalf of another party, that fact must be clearly enunciated.
4. Registrants must avoid conflicts of interest; if any arise, it must be disclosed to the employer or client. Compensation must be above board and only for services performed. (No acceptance of bribes, perks, kickbacks, etc.)
5. Registrants must be honest in all matters regarding their professional qualifications.
6. Registrants must conduct themselves honorably, responsibly, ethically, and lawfully in a manner to enhance the profession of engineering. State licensing boards have the power to fine and suspend engineers violating the aforementioned rules or assisting others to violate the rules. Suspension typically can also occur if the registrant is convicted of a felony or has had his/her license suspended in another state (for cause). Suspension or fines can also occur for nonpayment of privilege tax (license fee), practice without a license, improper use of seal (validation of designs not done by the engineer), and so forth.

23.6 CODES OF ETHICS

Most major societies prominently post and endorse a code of ethics. In general, these amount to reiterations and refinements of the aforementioned rules of professional conduct.

The IEEE code of ethics has 10 points; the IEEE makes explicit the additional ethical rules of nondiscrimination, rules against slander, and acceptance of criticism and actions needed for correction, and suggests the role of mentor for associations with coworkers. (See http://www.ieee.org/about/corporate/governance/p7-8.htmlfor details.) The NSPE (see http://www.nspe.org/resources/pdfs/Ethics/CodeofEthics/Code-2007-July.pdf) reiterates the aforementioned NSPE list as six fundamental canons. They then refine and expand each of these terms in a "rules of practice" section which is then followed by an interesting section on professional obligations. This section suggests such topics as participation in public affairs for the common good and publication in the lay press, along with sections that further refine the aforementioned rules of practice section. The NSPE site further has links to case studies and the engineers' creed.

Several online websites offer links to codes of ethics and case studies. One of the larger relating to engineering is http://www.onlineethics.org/. Should the need arise, this center offers assistance in solving ethical questions.

23.7 FORENSICS AND CONSULTING

At some point in many engineers' careers, they may acquire sufficient knowledge in an area that they can become forensic engineers and/or consulting engineers. Both can be very interesting and

highly remunerative careers. Anecdotally, "it takes 10 years to become an expert"; this length of time should be adequate to develop your skills to the point of expertise.

Forensic engineers typically research, in order to assist in the determination of "fault," the cause of an accident. Finding fault or placing blame allows one to proceed with litigation, if necessary or justified. In the field of BME, cases can run the gamut from determination of the potential for injury in a low-speed auto accident to the determination as to who is at fault for a death due to an air embolus. The first case would require that the engineer be well versed in biomechanics and accident reconstruction and the databases maintained on automobile accident injuries. The second case would require an in-depth look at all the instrumentation used in the case, the personnel involved, all records kept, and so forth.

A typical case involving a medical device accident involves an initial telephone contact between a lawyer (or sometimes a relative of the injured party) and the engineer (or firm). (Paper and/or e-mail contacts are not generally used, as this material is "discoverable.") The lawyer typically will have found you via your reputation in a given area (via referrals from others) or will have worked with you in the past. The lawyer will typically ascertain your level of knowledge in the area needed and should also be concerned regarding your licensure. An initial familiarization with the accident being investigated is strongly recommended prior to accepting the case, in order to determine if one has the credentials and the desire to pursue a given case. This may involve a review of the operative notes from a case or other documentation involving the injury or death. An hour or two of study should allow one to accept or decline a case. If the engineer agrees to investigate, details such as timing (when might this go to court, how fast a response is needed, etc.) and payment schedule (rates per hour, contingencies, expense payments, etc.) need to be agreed to. Other details, such as the need for access to records and devices, need to be taken care of as soon as feasible.

A personal philosophy regarding acceptance of cases should be developed. For example, the question "Can my work ameliorate some of the harm done to the client?" might be a useful guideline. "Is this going to be an interesting case?" might be another. "Might the results of this case result in improvement of the device or process involved?" "How much can I make?" flies in the face of the aforementioned ethics descriptions and is not professional.

There is no typical investigation. A broken device may be investigated and similar failures documented with data taken from the Food and Drug Administration (FDA) medical device and user facility device (MAUDE) database system. The clinical engineering services group in a related hospital may be queried about similar incidents. The device in question may be linked up to a patient simulator in order to determine error conditions in an assumed scenario. Determination of the fault is often a function of the imagination and resourcefulness of the investigating engineer.

In a significant fraction of cases, the engineer will find fault with the conduct of the clients of the lawyer who retained the engineer, at which point the engineer is typically relieved of further duty and employment on the case. If the data obtained are sufficient for the case of the employer, negotiations will often become the job of the lawyer, with an out-of-court settlement generally a goal. A step in this process may (or may not) involve the generation of a document under "Rule 26 (a federal statute)," in which your opinion regarding a case may be requested in a document that introduces your case and then outlines your qualifications, fees, and materials reviewed and summarizes your opinion at this time. Another step in this process might also involve a request by the opposition lawyer for a copy of all documents you have generated for a case; it thus behooves one to keep clean notes without bias.

Rarely do cases make it to trial. When and if they do, it behooves the engineer to have the credentials of licensing and adequate proof of experience with the device or process in question. A good command of the facts in question and the ability to accept questioning under stressful circumstances is also of value, to put it mildly.

A typical hourly rate for a forensic engineer is on the order of 1/1000 of the engineer's annual gross salary, or more. Daily rates generally are capped at 1/100 of the annual salary in order to not overcharge for time spent waiting for a court appearance, traveling, and so forth. Other reasonable

fees (mileage, meals, and hotel) are charged as applicable. Additional charges (for technician help, etc.) need to be negotiated in advance. With fees in this range, the engineer's fees will be near, but typically slightly lower than, the lawyer's fees.

Consulting practices generally involve the use of an expert in a particular area as an assistant in the solution of a "closed-end" problem. Thus, an expert in optics might be hired by an anesthesia machine development company to assist in the correction of a system to measure CO_2 in expired air. An expert in bioinformatics may be asked to advise on the development of a new database system. A biotechnologist may be called in to help advise on a new pharmaceutical generation system.

Consultants can be paid on an hourly basis, with rates negotiated by the consultants. These are often higher than those of the forensic engineer, due to the specialization of the task(s). Often, consultants are kept on a retainer basis and their expertise requested on an as-needed basis.

23.7.1 Consulting Example One

This author (Fries) was hired several times to audit a company's ability to meet the software standard IEC 62304. Each company was interested in listing certifying that they complied with the IEC standard on their 510(k) application. This saved them paperwork during the submission and delayed the inspection of their documents until the FDA auditor made his next visit. The work involved visiting the company's engineering spaces, visiting with software developers to discuss the software development process, and reviewing all documentation involved with the device. The process took 2 days in the company's spaces. Then the information collected was placed in a report sent to company and engineering management.

Consulting in this manner not only allows the consultant's expertise to be exhibited, but it is also a great learning experience for the consultant. It is also a great learning experience for the software developers, as they are always interested in what other companies are doing and how they are doing it. They are also interested in learning the best way to interface with the FDA auditor.

23.7.2 Consulting Example Two

This author (Fries) was hired to review a current ventilator that had been operating in the field for some time and then to review the new ventilator design and to make suggestions for improvement. The first step was to visit the company to do a hands-on review of the current ventilator. The next step was to review all failure data on the ventilator, especially how the device failed, when in the life cycle of the ventilator it failed, and how the failure was addressed. The author was also interested in any recalls on the ventilator that had been imposed by the FDA. The failure data were then plotted on graph paper to show the occurrence of the failures, the time of manufacturing of each failure, and the length of usage until the failure occurred.

Once that was complete, the review of the new design began. Design drawings were reviewed, prototypes were looked at, software code was reviewed, and any test data were examined. Suggestions for design changes, new testing, and changes for manufacturing and servicing ease were made. Time in the company spaces was 2–3 days, depending on the amount of documentation to review. Once completed, the data were placed in a report sent to company and engineering management, including suggestions for design and testing improvements.

As a consultant, you learn a lot from visiting various companies. The biggest caution you must take is to honor the confidentiality of data from each company. You can make generalities in your discussions, but you must never violate the confidentiality of any company.

23.8 CONTINUING EDUCATION

In order to maintain licensure, most states (over 30) require that licensed engineers obtain a minimum of relevant continuing education hours per year (24 hours per year, for example, in Tennessee).

These may be via attendance (sometimes with presentation) at technical or professional meetings, via seminars (corporate or correspondence), or via attendance in college or university courses. The courses must be relevant to the practice of engineering as the licensee practices it.

Membership in at least one relevant society and attendance at one 3-day society meeting per year would meet this minimum requirement and is strongly recommended. Additional attendance at trade shows and related seminars (for example, the Medical Design and Manufacturing [MD&M], MedTech (Medical Technology) Conference, and related shows, at 40+ world sites) is highly recommended as a means of staying current. Staying current is necessary in this competitive world.

EXERCISES

1. Perform a web search using the terms *engineer* and *code of ethics*. Briefly document the number and variety of sources you find.
2. Perform a web search using the term *forensic engineering*. Summarize your data. Discuss one firm or case of interest to you.
3. As a forensic engineer, you are called in on a case to determine how air entered a patient who was undergoing heart catheterization. What sources would you use to determine the cause of death?
4. As a forensics engineer, you have been let go by the client that hired you, as your results were not conducive to them winning their case. The opposition lawyers ask to hire you. What is your answer, and why?
5. You have submitted a written report detrimental to the company that hired you as a consultant. Their lawyer asks that all further discussions with them be oral rather than written. Why?
6. Search the web for the details on licensure in your home state. Compare to those mentioned in the text (Tennessee).

24 Concept to Product?

Change is inevitable, except from a vending machine.

Robert C. Gallagher

24.1 INTRODUCTION

This chapter is purposely titled with a question mark, as it is written to assist and advise you, the reader, in determining if you wish to take your concept as developed in your coursework, profession, or otherwise to a point where you decide to develop your final product. It is written to assist you in the early stages of such an endeavor. Such stages include determining if you personally are the right person for a product development. Funding issues may be paramount at different stages of your work. Decisions will need to be made on how funding will be acquired for each stage of your work (if at all). Licensing versus self-development will be a major issue. Intellectual property ownership issues may further be a concern. Marketing of your concept and later (presumably) of your product needs to be considered.

You will need to additionally answer the following questions: Am I an entrepreneur? Is this going to be my cause (for a month or years)? Is it worth it to me to pursue this project?

The material that follows is meant to give you some general guidelines prior to your possible commitment to development of a final product and help guide you to more comprehensive sources of assistance. The chapter will conclude with four examples of product developments.

24.2 PREPARE YOURSELF PRIOR TO ANY FURTHER DEVELOPMENTS

This chapter is written under the assumption that you have developed a concept for production (device or process, also termed *invention*) that you wish to take to market and that you have covered much of the other material in this text, especially the material in Chapter 20 (Licensing, Patents, and Copyrights) and Chapter 5 (Product Documentation). You have given serious consideration to items that can stop your innovation from making it to market, such as are elaborated in the text *Creative People Must Be Stopped*, which lists the following six innovation constraints (expansions are this author's):

1. Individual—Can you articulate your goals, be creative, convince others, and persevere?
2. Technology—Does the technology exist to support the product, or can it be developed in time?
3. Societal—Is there a need for this product, or will one develop?
4. Industry—Is this product innovative enough that it will outdistance the competition, or do I have to worry about this in planning?
5. Group—Do I have the right team to do this?
6. Organizational—Do we have the right development plans?

Successful product developments, according to the author, are those that lie in the Venn diagram intersection of all the aforementioned constraints. The Segway thus was not very successful as the average users' needs (societal constraint) were much more easily met with a bicycle or their own

feet. Kodak lost out on their own developed digital photography as a market as they misjudged the technological market, not realizing that users would be happy with a "good-enough" form of fast photography.

The following items need also to be reviewed.

24.2.1 Web Resources

If you have control of your invention and are considering selling the idea, spend some time on the Federal Trade Commission's (FTC's) website. The FTC is charged with preventing fraud and deceptive and unfair business practices in the marketplace. As such, the FTC has a good discussion of "invention promotion firms" and things to consider if contacting a firm to promote or buy your invention. Many do not deliver as promised (http://www.ftc.gov/bcp/edu/pubs/consumer/products/pro21.shtm12/4/2012).

You may wish to visit http://www.inventionconvention.com/ncio if your invention is patented to obtain up-to-date advice on protecting your patent as well as continuing development of your invention. The United Inventors Association website (http://www.uiausa.org/) also gives good advice and links to possible local inventor assistance. Inventnet (http://www.inventnet.com) has a good and readable discussion of invention development and marketing scams (http://www.inventnet.com/scam.html) worth reading. A listing of "suspected companies" is part of the article.

The Technology, Entertainment, Design website (http://www.ted.org) offers numerous brief but excellent talks by a number of people in industry and academia. Several of the talks are from designers who have taken their ideas to market and who therefore might be a model for you to emulate. A review of, for example, a talk entitled "Cheap All-Terrain Wheelchair" or "Universal Anesthesia Machine" might be relevant to your project. A few of the talks discuss the processes of taking an idea to market and may be especially useful.

24.2.2 Written Sources

Avail yourself of your library and survey the magazine racks and stacks. Spend some time looking through the magazine *Entrepreneur* for insights into people who started businesses similar to what you are considering. (Or review their website, http://www.entrpreneur.com.) Ditto with *Inc. Magazine* (or visit their site, http://www.inc.com). Also useful, dependent on your project, are *Fortune Magazine*, *Fast Company Magazine*, *MIT Tech Review*, and various consulting group publications.

Far more comprehensive than the coverage in this text (for commercialization) is the material in *Biodesign, the Process of Innovating Medical Technologies* (Cambridge University Press, 2010), especially the material in Chapter 6, "Integration," which discusses operating plans and financial models, business plan development, funding sources, and licensing and alternate pathways for projects such as you might be developing. Much of this material is also available on the text website, http://www.ebiodesign.org, and is available for use. The website is maintained by the authors at Stanford University and is highly recommended by the authors of this text.

24.2.3 Personal Contacts—Networking and Conferences

Attend one or more conventions dealing with entrepreneurship and business promotion.

A good example is the National Council of Entrepreneurial Tech Transfer (NCET2) meeting. NCET2 is an organization of entrepreneurial universities creating and funding university startups. NCET2 promotes best practices in the creation and funding of university startups by supporting entrepreneurship and providing entrepreneurial education. NCET2 connects investors, economic development organizations, public and private funds, and tech transfer professionals in building communities of innovation at universities. NCET2 provides an annual conference for innovation stakeholders to share experiences and create a constructive dialog on how to best work together.

Sponsoring organizations include the National Science Foundation, the U.S. Department of Health and Human Services National Institute of Health Office of Technology Transfer, the National Venture Capital Association, Angel Capital Association, and others. Attendees include university tech transfer personnel, Angel and corporate investors, Fortune 500 and other companies, nonprofit representatives, and entrepreneurs. Topics discussed are the Small Business Innovation Research (SBIR), university incubators and accelerators, venture philanthropy, global issues, crowd funding, and entrepreneurial support mechanisms.

The annual National Collegiate Innovators and Inventors Association (NCIIA) is a good meeting to attend if you are associated with one of the many universities that sponsor the meeting (along with the Lemelson Foundation; see http://NCIIA.org and/or http://lemelson.org).

Visit your technology transfer office (if at a university) to discuss possible support or get advice. Visit your school of management if applicable. Ditto your law school. Ditto any friends/acquaintances who have developed their own product or process.

24.2.4 Introspect

Look at your desire and motivations for this project. Look at your competencies. Try to make a rational choice now, as you see fit. Leave yourself open to future changes as necessary.

- Some of the questions and considerations you need to review are as follows: At this point of your work, you have developed a concept and a justification for taking the concept to at least a prototype embodiment (Chapters 1 through 6 or so). Answer the following questions: How strongly do I feel about my project? Do I have the ability to generate a convincing elevator pitch (a 0.5–2 minute talk) to sell my idea? If needed, can I generate a logical written plan that would convince NSF, SBIR, or Small Business Technology Transfer (STTR) reviewers to fund my work?
- Do I personally have the competencies to pursue this project from this point on to sales and maintenance of my product? If not, at what point will I call in partners to assist in further development and/or manufacture and/or sales, and so forth? Or will I be satisfied at taking the product to the point that I can license (sell) the technology and get my life back?
- Failures far outnumber successes. Am I willing to chance failure to pursue my dream? Am I willing to spend weeks/months/years (choose one) to achieve this?

If you answered yes to all of the aforementioned, label yourself an entrepreneur and get to work.

24.3 FIND FUNDING SOURCES

The amount of funding needed—obviously—will depend on your living expenses and the particular project you have embarked upon and the snags hit during development, production, and marketing phases. The list that follows is a partial set of suggestions.

24.3.1 Family

This author has heard of an entrepreneur who mortgaged his grandmother's house to raise money for a project. Luckily, that person was successful and was not a topic for the TV show *American Greed*. Be very wary of expectations for payback and the possibility of losses.

24.3.2 University

If your invention was university based, you may have the option to utilize its funding and other assets, such as incubator spaces. If applicable, be sure to check this out. Be sure that you are clearly

not obligated to involve your university if there is any potential claim they might have. While your return might be smaller if your university does all the work (for example, takes your idea and licenses it), you should get compensation without all the headaches of marketing a project. Visit (in person or via the web) your university technology transfer office to discuss their (potential) roles in support of your work.

24.3.3 Government

As previously mentioned, the NSF, SBIR, and STTR programs are available and may be applicable to your effort. Twelve different agencies of the federal government have SBIR and STTR granting programs. The STTR program is aimed at collaboration between small businesses and research institutions, while the SBIR program is aimed primarily at small businesses. Both offer significant funding opportunities in specific areas supported by the individual agencies. See http://www.sbir.gov/for more details.

24.3.4 Private Agencies

There are a number of private agencies that will support specific areas of endeavor. The NCIIA, for example, supports collegiate "e-teams" with funds to begin a design experience and with funds to continue projects if a complete-enough justification is generated. With over a million charitable organizations in the United States, you will need to search these with a reasonable filter (http://nccs.urban.org/).

24.3.5 Angel Investors

This is a well-heeled business investor (or group) that is willing to invest in endeavors meeting their criteria. They may be found at conferences such as NCET2, the NCIIA annual meeting, etc. If you are at a university, the technology transfer office may be familiar with some. Your local business associations or government panels or bankers may also assist in introductions. (See also the *Inc. Magazine* site, http://www.inc.com/guides/start_biz/24011.html, and the National Venture Capital Association, http://www.nvca.org.)

24.3.6 The Web

Crowd funding is now an option for starting a business. One of the more successful and publicized to date is Kickstarter (see http://www.kickstarter.com/). If accepted, you may obtain funding from individuals in return for a one-time "thank you" of your choice.

The aforementioned comprises the majority of means to obtain cash for your project. The sweat will be all yours and your coworkers'.

24.4 NEXT STEPS

Assuming your product continues to launch, you will need to make many decisions along the way. Some of the major ones will be as follows: Quit or continue. License or build myself. Continue as CEO and/or as inventor/developer. Hire a marketer or do it myself. Form a company to enable a legal status for this effort. Hire a consultant to assist in developing the product or assist in meeting regulatory requirements. Find a manufacturer. Maintain the product or outsource it. Obtain assistance in pricing. Obtain legal counsel. Get a degree in management. And so forth.

This text cannot but introduce the subject of what's next regarding your device or project. We can best wrap up with a few examples of design projects that have gone to market.

24.5 CASE STUDY: PATHFINDER TECHNOLOGIES

By the year 2007, Dr. Robert Galloway at Vanderbilt University and his team had had 20 years of experience developing hardware and software techniques for the process of image-guided surgery. He and other engineering faculty had linked up with a physician and had tested their system on at least 20 operating room (OR) procedures on neurosurgery patients and over 200 on liver tumor resection patients.

They had learned some of the details necessary to translate technology from the engineering school environment to the OR environment. Specifically, they had learned to accept and act upon feedback from the surgeon in charge. Further, they had gotten to the point of understanding the finer details of workflow in the OR environment, such as when and how images were taken to guide the surgeon and how their device could be placed safely in the OR environment before, during, and (removed) after surgery. Third, they had begun to understand that their relationships with ancillary personnel that were involved in the OR are environment. Lastly, they had accepted the fact that they were part of the OR team and were to be judged upon not just their daily performance but also their worst performance.

The expressed interest of a commercial company in the refinement, marketing, and licensing of the technology developed caused the team to try to put together a plan for their part in continued development and refinement of their device for this company. Approximately 9 months of effort were expended in the development of plans, budgets, and technology development protocols in order to work up a reasonable contract with the company. Bluntly put, the company backed out of the negotiations as the company apparently did not want to invest in continued device/process development but, rather, preferred to take a device directly to market.

With the inspiration of a feasibility and market study done on the device by some management students, the principals approached a venture capitalist with figures based upon the product development studies. With the estimated figure of a gross market of between $1 billion and $8 billion, the interest of Vanderbilt's office of technology transfer was also piqued.

Over the next several years, Dr. Galloway had multiple experiences. With a licensing agreement in hand, he had to decide how to proceed with the development of his work in a feasible fashion. Part of his successful path involved obtaining SBIR support. This provided some of the interim funding needed to continue development of their hardware and software to the point that it could be written up for Food and Drug Administration (FDA) consideration and approval. He had to face, as many inventors do, a decision as to his willingness (and drive) to be the CEO of the emerging company. Preferring to remain an academic, he assisted in selecting a CEO and, later, a COO, who, in fact, had been a past student of his.

By 2007, in addition to the lessons learned previously, Dr. Galloway passed on a few additional comments regarding development of his system. His experience as an academic had taught him how to budget for the academic environment; his experiences in trying to translate technology from academia to industry suggested that the recommended budget needed to be higher by at least a factor of four. Maintenance of your rights to your invention must be protected via proper notebooks, proper disclosures (notarized), copyright as necessary, and so forth. Team effort and camaraderie and joint ownership must be protected. Lastly, there is no one better qualified to develop your invention than you if you are willing to do so (as an active member of the team but not necessarily as CEO).

As of this writing, Pathfinder Technologies is being advertised and refined. To read up on the developed technology, the reader is referred to the website http://www.pathnav.com.

24.6 NCIIA EXAMPLES

As mentioned earlier, the NCIIA (http://www.nciia.org) is a source of funding for many undergraduate- and graduate-level projects (not just in biomedical engineering [BME] or bioengineering [BioE]). The reader is referred to the website http://www.nciia.org/companies_launched for a listing

of the over 80 companies formed as a result of their grant funding of undergraduate- and graduate-level projects. The two examples that follow should give the reader a feeling for what can be done, starting with seed funding from the NCIIA and initial guidance from faculty and team members, and hard work on the part of the developers.

24.6.1 The EpiCard E-Team

The EpiCard E-Team at the University of Virginia received funding of $13,769 for their e-team proposal to the NCIIA to develop a credit card–sized automatic epinephrine injection system. From the NCIIA website description (http://www.nciia.org/node/734, reprinted with permission of the NCIIA):

> Millions of people are diagnosed with life-threatening allergies each year, and in extreme cases, these allergies can cause a deadly anaphylactic response. To combat anaphylaxis in an emergency situation, allergic individuals carry a life-saving injectable dose of epinephrine; however, epinephrine injectors currently on the market are too bulky and a hassle to carry, and as a result, less than half the people who should carry an injector on them at all times actually do so. To answer this problem, the EpiCard E-Team, now formally incorporated as Intellijject, Inc., has invented an *automatic epinephrine injecting system* that is *credit-card sized* and easy to use. The EpiCard can be carried almost anywhere—in the user's purse, wallet, or pocket—and is efficient and safe.
>
> The Virginia-based company has now received nearly $13 million in funding from various sources. Visit intellijject.com for more information.
>
> **Update:**
>
> - In 2009, Intellijject announced an exclusive license worth $230 million with Sanofi-aventis U.S. for a novel epinephrine auto-injector, in the U.S. and Canada territory. Under the license, Sanofi-aventis U.S. shall be responsible for manufacturing and commercialization. Intellijject will be responsible for the on-going development and for obtaining U.S. regulatory approval and has retained certain co-promotion rights in the territory.
> - February 2012: Evan and Eric Edwards and their product, now called Auvi-Q, were featured in the NY Times (http://www.nytimes.com/2013/02/02/business/auvi-q-challenges-epipen-with-a-new-shape-and-size.html?emc=eta1&_r=0).

A detailed description of the "lessons learned" from their experiences may be found at http://www.nciia.org/taxonomy/term/608 and is recommended reading for those interested in their path to market.

24.6.2 Nanografts

The BME-IDEA Competition winner in 2006 was the team Nanografts from the University of California, Berkeley. The project description from the NCIIA website reads as follows (http://www.nciia.org/node/1436, reprinted with the permission of the NCIIA): "With over 500,000 performed each year, coronary artery bypass surgery is the default procedure for people with severe heart disease. But the surgery, in which doctors remove a healthy blood vessel from the patient's arm or leg and use it to build a detour around a blocked artery in the heart, isn't without its drawbacks: 50% of vein grafts fail in 5–10 years, the surgery to harvest the vein is expensive and invasive, and some patients have veins that simply aren't strong enough to act as a coronary bypass graft."

Synthetic grafts have long held promise as a way to improve on the vein graft, but have yet to be widely implemented. The biggest reason? They're too big. The smallest currently possible diameter for a successful synthetic graft is around 5 mm—too large to replace most coronary arteries, which range from 2–6 mm. Additionally, many of today's synthetic grafts are made from foreign materials that can be rejected by the body's immune system, rendering them ineffective. It all adds up to a problem; or, looked at another way, an opportunity for innovation.

Craig Hashi is the innovator. The Berkeley BioE PhD student, leader of the Nanografts team that grabbed first place in the 2006 BME-IDEA competition, has come up with a novel approach to synthetic grafts. He creates sheets made from polymer nanofibers, then seeds the sheets with the patient's own bone marrow stem cells. The stem cells allow the sheets to mimic the native blood vessel tissue, reducing the risk of being rejected, and the nanofibers allow the building of grafts as small as .7 mm in diameter. After letting the cells grow for a couple of days, the sheets are rolled into a tube, similar to the shape of an artery. Once implanted, the nanofiber tube degrades, leaving a fully functioning blood vessel.

Sound clean and simple? Not so much. Although Nanografts has certainly made progress since winning BME-IDEA funding, continuing their lab research and talking with venture capitalists, the biggest challenge remains the technology itself. This is radical stuff—giving the body the capability to grow wholly new veins—and will take time to develop. Says Hashi, "Right now, the biggest challenge we face is getting the technology to work—understanding what's really going on with it. I've been finishing up a paper on the project, but we want to make sure we're confident about the technology before we present something to the research community—we want to be able to show exactly how these stem cells work and what they do."

Beyond the technical challenges, there are problems with using stem cells themselves. Due to the surgery timeline (the patient may not be able to wait several days for stem cells to grow), potential cost factors, and strict FDA regulations, the team believes moving away from a stem cell-based approach for the moment gives them the best shot at commercialization. "We understand that in order to commercialize this in the near future we'll have to steer away from cell-based therapy," says Hashi. "Adding stem cells is an extra step that slows down the implantation process, to say nothing of regulatory issues. But if you have a synthetic graft that's readily available off-the-shelf, the surgeon can use it right away and implant it directly."

Although the science is still in the early stages, Hashi has a plan for how to commercialize Nanografts. "Ideally, we'll start with some small seed rounds, about 150–200k," he says. "We'll work six to nine months with that, and then hopefully talk to some more VCs, get a term sheet, and get in contact with people that can provide us with more corporate experience, more managerial direction. From there we take it to market."

Participating in the BME-IDEA competition has given Hashi a way to connect with those VCs. "Getting national exposure as a result of winning the competition has gotten us a lot of attention that we wouldn't have received otherwise," says Hashi. "It really gives me credibility when I walk into a VC's office. I can say, 'I just won BME-IDEA, a national biomedical design competition. My team went through a rigorous competitive process and we were fortunate to win first place.' It gives me not only confidence and credibility but a great way to begin the conversation."

Update: The team, now incorporated as Nanovasc, received $4.7 million in venture capital funding in 2008.

The company has since had three SBIR awards (2009, 2010, and 2011) to continue development of their product.

24.7 DEVELOPMENT OF MAX MOBILITY CORP., MARK RICHTER, PHD, PE, OWNER

As a final example of entrepreneurship for this chapter, we will use the company Max Mobility and its president, Mark Richter.

Mark received his PhD from Stanford University in the year 2004 in mechanical engineering. His thesis topic was "Handrim Compliance and the Wheelchair User." Mark's dissertation was concerned with decreasing injuries in patients using wheelchairs by investigating the effect of the hand rim on the propulsion of the wheelchairs.

Mark's career in rehabilitation engineering began in 1995, when he was a mechanical engineering intern at the Lucille Packard Children's Hospital Rehabilitation Engineering Center in Stanford, California. His initial work involved design of a myoelectric-actuated upper extremity prosthetic training aid for children. His work also involved developing a collapsible cuff crutch prototype.

From 1995 to 2000, Mark was a research engineer with the company Beneficial Designs Incorporated working out of Santa Cruz, California. Mark worked on three projects over this time period: his later PhD project, low-impact wheelchair hand rim design; surface characteristics for accessibility measurements; and hand strength assessments for quantification of wheelchair users' ability to propel themselves.

From 2001 to 2005, Mark worked in Nashville, Tennessee. He developed a bio-mobility laboratory as an extension of his work for Beneficial Designs Incorporated. He undertook several new projects at this time. He developed an instrument canoe paddle to help analyze paddling forces during use of canoes! He developed a device named "GripRim" to improve the ability of wheelchair users to grip the wheelchair rims. He developed a low-impact hand rim named "FlexRim" with the goal also of improving wheelchair propulsion. He further worked on a device termed "OptiFit," which is a product to assist wheelchair prescribers and clinicians in obtaining subject measurements to determine the optimal seating configurations and dimensions for prescribed wheelchairs. Mark also developed a device to measure foot trail accessibility for wheelchair users. The device consists of a trail cart with GPS and cart orientation and user data collection software (UTAP Pro). Mark was also active in part-time investigation of product liability legal cases relating to assistive technology products and services. In addition, he was also involved in assisting in the development of various standards relating to assistive technology.

As mentioned elsewhere in this text, it takes about 10 years to become an expert in any given area. By the year 2005, Mark had had about 10 years of experience working in the area of rehabilitation engineering and was in a position to consider being master of his own destiny in terms of research, goals, and paycheck. Thus, in 2005, Mark formed the company Max Mobility in Antioch, Tennessee. The company undertakes projects aimed at maximizing the mobility of persons with disabilities. It is currently housed in an 8000 ft.^{2} facility with a wheelchair propulsion biomechanics laboratory, a prototyping shop, office space, and storage space. The company currently employs 10 engineers with advanced degrees.

The company currently has three major products and it investigates wheelchair propulsion dynamics. One project/product is termed "OptiPush," which is a developmental system with the goal of improving cardiovascular fitness, exercise capability, and strength for wheelchair users. The physical system is composed of a wheelchair-accessible treadmill training system with computerized feedback to assist in optimal pushing of the wheelchair under different speed and slope conditions. Additionally, the company investigates multiple means of reducing physical demands on wheelchair users under differing environmental conditions.

A second product is termed "ErgoChair." This is a device that allows modification of the wheelchair seat height in order to ergonomically improve working conditions involving lifting tests and wheelchair transfers. A recent third product is a detachable battery assistive propulsion device ("SmartDrive," trademarked). This product nicely fills the niche between a completely manual wheelchair (a few hundred dollars) and a fully powered wheelchair (thousands of dollars) with an insurance-reimbursable few-hundred-dollar assistive technology. The technology consists of a battery pack that fits under the wheelchair seat and an attachment driver (as shown in Figure 24.1) that locks onto the rear axle guard of the wheelchair. The assistive device (brake to control, other control methods under development) allows the user to more easily climb inclines and move over grass and carpets.

Funding for the company's research has come primarily from government support through National Institutes of Health (NIH), NSF, and U.S. Department of Agriculture (USDA) grant support (12 to date). Most of this support has been under SBIR grants. Some current funding and planned future funding will additionally come from sales of the products mentioned.

FIGURE 24.1 SmartDrive installed on a user's wheelchair.

Some of the developmental work has also been accomplished via collaborative project support with local universities. Two from Tennessee State University obtained their master's degree working on projects with the company. One student at Vanderbilt obtained his PhD for project work in developing instrumentation for wheelchair mobility measurements. Over 20 undergraduate student design projects have been sponsored with local university student groups. To date, six patents have been granted for intellectual property developed, and two additional are pending.

This company has now been in existence for 8 years. It is an example of what can be done with directed engineering skills and motivation. The company's website is http://max-mobility.com/.

Mark's advice: being your own boss is a hard, long road, but it is worth it for the good you can do for others.

24.8 CONCLUSION

The intent of this chapter has been to introduce you, the reader, to the possibility of developing your product idea or concept to a tangible end product as a result of your labor and assistance from various sources. Financial success and service to the public can be your reward.

SUGGESTED READING

Galloway, R. L., "Found in Translation: From the Laboratory to the Operating Room to the Market," in *Proceedings of the 29th Annual International, Conference of the IEEE EMBS, Cité Internationale, Lyon, France*, August 23–26, 2007.

NCIIA Publication: *Getting Started as an Entrepreneur—A Guide for Students,* 2002.

Owens, D. A. *Creative People Must Be Stopped, 6 Ways We Kill Innovation*. Wiley Press, 2012.

Zenios, S., Makower, J., and Yock, P. *Biodesign, The Process of Innovating Medical Technologies*. Cambridge University Press, 2010.

Appendix 1: χ^2 Table

υ/ϒ	0.975	0.950	0.900	0.050	0.100	0.050	0.025
1	0.001	0.004	0.016	0.455	2.706	3.841	5.024
2	0.051	0.103	0.211	1.386	4.605	5.991	7.738
3	0.216	0.352	0.584	2.366	6.251	7.815	9.438
4	0.484	0.711	1.064	3.357	7.779	9.488	11.143
5	0.831	1.145	1.610	4.351	9.236	11.070	12.832
6	1.237	1.635	2.204	5.348	10.645	12.592	14.449
7	1.690	2.167	2.833	6.346	12.017	14.067	16.013
8	2.180	2.733	3.490	7.344	13.362	15.507	17.535
9	2.700	3.325	4.168	8.343	14.684	16.919	19.023
10	3.247	3.940	4.865	9.342	15.987	18.307	20.483
11	3.816	4.575	5.578	10.341	17.275	19.675	21.920
12	4.404	5.226	6.304	11.340	18.549	21.026	23.337
13	5.009	5.892	7.042	12.340	19.812	22.362	24.736
14	5.629	6.571	7.790	13.339	21.064	23.685	26.119
15	6.262	7.261	8.547	14.339	22.307	24.996	27.488
16	6.908	7.962	9.312	15.338	23.542	26.296	28.845
17	7.564	8.672	10.085	16.338	24.769	27.587	30.191
18	8.231	9.390	10.865	17.338	25.989	28.869	31.526
19	8.907	10.117	11.651	18.338	27.204	30.144	32.852
20	9.591	10.851	12.443	19.337	28.412	31.410	34.170
21	10.283	11.591	13.240	20.337	29.615	32.671	35.479
22	10.982	12.338	14.041	21.337	30.813	33.924	36.781
23	11.688	13.091	14.848	22.337	32.007	35.172	38.076
24	12.401	13.848	15.659	23.337	33.196	36.415	39.364
25	13.120	14.611	16.473	24.337	34.382	37.652	40.646
26	13.844	15.379	17.292	25.336	35.563	38.885	41.923
27	14.573	16.151	18.114	26.336	36.741	40.113	43.194
28	15.308	16.928	18.939	27.336	37.916	41.337	44.461
29	16.047	17.708	19.768	28.336	39.087	42.557	45.722
30	16.791	18.493	20.599	29.336	40.256	43.773	46.979

Appendix 2: Percent Rank Tables

Sample Size = 1							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	2.50	5.00	10.00	50.00	90.00	95.00	97.50

Sample Size = 2							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	1.258	2.532	5.132	29.289	68.377	77.639	84.189
2	15.811	22.361	31.623	71.711	94.868	97.468	98.742

Sample Size = 3							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.840	1.695	3.451	20.630	53.584	63.160	70.760
2	9.430	13.535	19.580	50.000	80.420	86.465	90.570
3	29.240	36.840	46.416	79.370	96.549	98.305	99.160

Sample Size = 4							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.631	1.274	2.600	15.910	43.766	52.713	60.236
2	6.759	9.761	14.256	38.573	67.954	75.140	80.588
3	19.412	24.860	32.046	61.427	85.744	90.239	93.241
4	39.764	47.287	56.234	84.090	97.400	98.726	99.369

Sample Size = 5							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.505	1.021	2.085	12.945	36.904	45.072	52.182
2	5.274	7.644	11.223	31.381	58.389	65.741	71.642
3	14.663	18.926	24.644	50.000	75.336	81.074	85.337
4	28.358	34.259	41.611	68.619	88.777	92.356	94.726
5	47.818	54.928	63.096	87.055	97.915	98.979	99.495

Sample Size = 6							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.421	0.851	1.741	19.910	31.871	39.304	45.926
2	4.327	6.285	9.260	26.445	51.032	58.180	64.123
3	11.812	15.316	20.091	42.141	66.681	72.866	77.722
4	22.278	27.134	33.319	57.859	79.909	84.684	88.188
5	35.877	41.820	48.968	73.555	90.740	93.715	95.673
6	54.074	60.696	68.129	89.090	98.259	99.149	99.579

Sample Size = 7							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.361	0.730	1.494	9.428	28.031	34.816	40.962
2	3.669	5.338	7.882	22.489	45.256	52.070	57.872
3	9.899	12.876	16.964	36.412	59.618	65.874	70.958
4	18.405	22.532	27.860	50.000	72.140	77.468	81.595
5	29.042	34.126	40.382	63.588	83.036	87.124	90.101
6	42.128	47.930	54.744	77.151	92.118	94.662	96.331
7	59.038	65.184	71.969	90.752	98.506	99.270	99.639

Sample Size = 8							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.316	0.639	1.308	8.300	25.011	31.234	36.942
2	3.185	4.639	6.863	20.113	40.625	47.068	52.651
3	8.523	11.111	14.685	32.052	53.822	59.969	65.086
4	15.701	19.290	23.966	44.016	65.538	71.076	75.514
5	24.486	28.924	43.462	55.984	76.034	80.710	84.299
6	34.914	40.031	46.178	67.948	85.315	88.889	91.477
7	47.349	52.932	59.375	79.887	93.137	95.361	96.815
8	63.058	68.766	74.989	91.700	98.692	99.361	99.684

Sample Size = 9							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.281	0.568	1.164	7.413	22.574	28.313	33.627
2	2.814	4.102	6.077	17.962	36.836	42.914	48.250
3	7.485	9.775	12.950	28.624	49.008	54.964	60.009
4	13.700	16.875	21.040	39.308	59.942	65.506	70.070
5	21.201	25.137	30.097	50.000	69.903	74.863	78.799
6	29.930	34.494	40.058	60.692	78.960	83.125	86.300
7	39.991	45.036	50.992	71.376	87.050	90.225	92.515
8	51.750	57.086	63.164	82.038	93.923	95.898	97.186
9	66.373	71.687	77.426	92.587	98.836	99.432	99.719

Sample Size = 10							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.253	0.512	1.048	6.697	20.567	25.887	30.850
2	2.521	3.677	5.453	16.226	33.685	39.416	44.502
3	6.674	8.726	11.583	25.857	44.960	50.690	55.610
4	12.155	15.003	18.756	35.510	55.173	60.662	65.245
5	18.709	22.244	26.732	45.169	64.578	69.646	73.762
6	26.238	30.354	35.422	54.831	73.268	77.756	81.291
7	34.755	39.338	44.827	64.490	81.244	84.997	87.845
8	44.390	49.310	55.040	74.143	88.417	91.274	93.326
9	55.498	60.584	66.315	83.774	94.547	96.323	97.479
10	69.150	74.113	79.433	93.303	98.952	99.488	99.747

Sample Size = 11							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.230	0.465	0.953	6.107	18.887	23.840	28.491
2	2.283	3.332	4.945	14.796	31.024	36.436	41.278
3	6.022	7.882	10.477	23.579	41.516	47.009	41.776
4	10.926	13.508	16.923	32.380	51.076	56.437	60.974
5	16.749	19.958	24.053	41.189	59.947	65.019	69.210
6	23.379	27.125	31.772	50.000	68.228	72.875	76.621
7	30.790	34.981	40.053	58.811	75.947	80.042	83.251
8	39.026	43.563	48.924	67.620	83.077	86.492	89.074
9	48.224	52.991	58.484	76.421	89.523	92.118	93.978
10	58.722	63.564	68.976	85.204	95.055	96.668	97.717
11	71.509	76.160	81.113	93.893	99.047	99.535	99.770

Sample Size = 12							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.211	0.427	0.874	5.613	17.460	22.092	26.465
2	2.086	3.046	4.524	13.598	28.750	33.868	38.480
3	5.486	7.187	9.565	21.669	38.552	43.811	48.414
4	9.925	12.285	15.419	29.758	47.527	52.733	57.186
5	15.165	18.102	21.868	37.583	55.900	60.914	65.112
6	21.094	24.530	28.817	45.951	63.772	68.476	72.333
7	27.667	31.524	36.228	54.049	71.183	75.470	78.906
8	34.888	39.086	44.100	62.147	78.132	81.898	84.835
9	42.814	47.267	52.473	70.242	84.581	87.715	90.075
10	51.586	56.189	61.448	78.331	90.435	92.813	94.514
11	61.520	66.132	71.250	86.402	95.476	96.954	97.914
12	73.535	77.908	82.540	94.387	99.126	99.573	99.789

Sample Size = 13							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.195	0.394	0.807	5.192	16.232	20.582	24.705
2	1.921	2.805	4.169	12.579	26.784	31.634	36.030
3	5.038	6.605	8.800	20.045	35.978	41.010	45.447
4	9.092	11.267	14.161	27.528	44.426	49.465	53.813
5	13.858	16.566	20.050	35.016	52.343	57.262	61.426
6	19.223	22.396	26.373	52.508	59.824	64.520	68.422
7	25.135	28.705	33.086	50.000	66.914	71.295	74.865
8	31.578	35.480	40.176	57.492	73.627	77.604	80.777
9	38.574	42.738	47.657	64.984	79.950	83.434	86.142
10	46.187	50.535	55.574	72.472	85.839	88.733	90.908
11	54.553	58.990	64.022	79.955	91.200	93.395	94.962
12	63.970	68.366	73.216	87.421	95.831	97.195	98.079
13	75.295	79.418	83.768	94.808	99.193	99.606	99.805

Sample Size = 14							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.181	0.366	0.750	4.830	15.166	19.264	23.164
2	1.779	2.600	3.866	11.702	25.067	29.673	33.868
3	4.658	6.110	8.148	18.647	33.721	38.539	42.813
4	8.389	10.405	13.094	25.608	41.698	46.566	50.798
5	12.760	15.272	18.513	32.575	49.197	54.001	58.104
6	17.661	20.607	24.316	39.544	56.311	60.959	64.862
7	23.036	26.358	30.455	46.515	63.087	67.497	71.139
8	28.861	32.503	36.913	53.485	69.545	73.642	76.964
9	35.138	39.041	43.689	60.456	75.684	79.393	82.339
10	41.896	45.999	50.803	67.425	81.487	84.728	87.240
11	49.202	53.434	58.302	74.392	86.906	89.595	91.611
12	57.187	61.461	66.279	81.353	91.852	93.890	95.342
13	66.132	70.327	74.933	88.298	96.134	97.400	98.221
14	76.836	80.736	84.834	95.170	99.250	99.634	99.819

Sample Size = 15							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.169	0.341	0.700	4.516	14.230	18.104	21.802
2	1.658	2.423	3.604	10.940	23.557	27.940	31.948
3	4.331	5.685	7.586	17.432	31.279	36.344	40.460
4	7.787	9.666	12.177	23.939	39.279	43.978	48.089
5	11.824	14.166	17.197	30.452	46.397	51.075	55.100
6	16.336	19.086	22.559	36.967	53.171	57.744	61.620
7	21.627	24.373	28.218	43.483	59.647	64.043	67.713
8	26.586	29.999	34.152	50.000	65.848	70.001	73.414
9	32.287	35.957	40.353	56.517	71.782	75.627	78.733
10	38.380	42.256	46.829	63.033	77.441	80.914	83.664
11	44.900	48.925	53.603	69.548	82.803	85.834	88.176
12	51.911	56.022	60.721	76.061	87.823	90.334	92.213
13	59.540	63.656	68.271	82.568	92.414	94.315	95.669
14	68.052	72.060	76.443	89.060	96.396	97.577	98.342
15	78.198	81.896	85.770	95.484	99.300	99.659	99.831

Sample Size = 16							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.158	0.320	0.656	4.240	13.404	17.075	20.591
2	1.551	2.268	3.375	10.270	22.217	26.396	30.232
3	4.047	5.315	7.097	16.365	29.956	34.383	38.348
4	7.266	9.025	11.380	22.474	37.122	41.657	45.646
5	11.017	13.211	16.056	28.589	43.892	48.440	52.377
6	15.198	17.777	21.041	34.705	50.351	54.835	58.662
7	19.753	22.669	26.292	40.823	56.544	60.899	64.565
8	24.651	27.860	31.783	46.941	62.496	66.663	70.122
9	29.878	33.337	37.504	53.059	68.217	72.140	75.349
10	35.435	39.101	43.456	59.177	73.708	77.331	80.247
11	41.338	45.165	49.649	65.295	78.959	82.223	84.802
12	47.623	51.560	56.108	71.411	83.944	86.789	88.983
13	54.354	58.343	62.878	77.526	88.620	90.975	92.734
14	61.652	65.617	70.044	83.635	92.903	94.685	95.953
15	69.768	73.604	77.783	89.730	96.625	97.732	98.449
16	79.409	82.925	86.596	95.760	99.344	99.680	99.842

Sample Size = 17							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.149	0.301	0.618	3.995	12.667	16.157	19.506
2	1.458	2.132	3.173	9.678	21.021	25.012	28.689
3	3.779	4.990	6.667	15.422	28.370	32.619	36.441
4	6.811	8.465	10.682	21.178	35.187	39.564	43.432
5	10.314	12.377	15.058	26.940	41.639	46.055	49.899
6	14.210	16.636	19.716	32.704	47.807	52.192	55.958
7	18.444	21.191	24.614	38.469	53.735	58.029	61.672
8	22.983	26.011	29.726	44.234	59.449	63.599	67.075
9	27.812	31.083	35.039	50.000	64.961	68.917	72.188
10	32.925	36.401	40.551	55.766	70.274	73.989	77.017
11	38.328	41.971	46.265	61.531	75.386	78.809	81.556
12	44.042	47.808	52.193	67.296	80.284	83.364	85.790
13	50.101	53.945	58.361	73.060	84.942	87.623	89.686
14	56.568	60.436	64.813	78.821	89.318	91.535	93.189
15	63.559	67.381	71.630	84.578	93.333	95.010	96.201
16	71.311	74.988	78.979	90.322	96.827	97.868	98.542
17	80.494	83.843	87.333	96.005	99.382	99.699	99.851

Sample Size = 18							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.141	0.285	0.584	3.778	12.008	15.332	18.530
2	1.375	2.011	2.995	9.151	19.947	23.766	27.294
3	3.579	4.702	6.286	14.58	26.942	31.026	34.712
4	6.409	7.970	10.064	20.024	33.441	37.668	41.418
5	9.695	11.643	14.177	25.471	39.602	43.888	47.637
6	13.343	15.634	18.549	30.921	45.502	49.783	53.480
7	17.299	19.895	23.139	36.371	51.184	55.405	59.007
8	21.530	24.396	27.922	41.823	56.672	60.784	64.255
9	26.019	29.120	32.885	47.274	61.980	65.940	69.243
10	30.757	34.060	38.020	52.726	67.115	70.880	73.981
11	35.745	39.216	43.328	58.177	72.078	75.604	78.470
12	40.993	44.595	48.618	63.629	76.861	80.105	82.701
13	46.520	50.217	54.498	69.079	81.451	84.336	86.657
14	52.363	56.112	60.398	74.529	85.823	88.357	90.305
15	58.582	62.332	66.559	79.976	89.936	92.030	93.591
16	65.288	68.974	73.058	85.419	93.714	95.298	96.421
17	72.706	76.234	80.053	90.849	97.005	97.989	98.625
18	81.470	84.668	87.992	96.222	99.416	99.715	99.859

Sample Size = 19							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.133	0.270	0.553	3.582	11.413	14.587	17.647
2	1.301	1.903	2.835	8.678	18.977	22.637	26.028
3	3.383	4.446	5.946	13.827	25.651	29.580	33.138
4	6.052	7.529	9.514	18.989	31.859	35.943	39.578
5	9.147	10.991	13.394	24.154	37.753	41.912	45.565
6	12.576	14.747	17.513	29.322	43.405	47.580	51.203
7	16.289	18.750	21.832	34.491	48.856	52.997	56.550
8	20.252	22.972	26.327	39.660	54.132	58.194	61.642
9	24.447	27.395	30.983	44.830	59.246	63.188	66.500
10	28.864	32.009	35.793	50.000	64.207	67.991	71.136
11	33.500	36.812	40.754	55.170	69.017	72.605	75.553
12	38.358	41.806	45.868	60.340	73.673	77.028	79.748
13	43.450	47.003	51.144	65.509	78.168	81.250	83.711
14	48.797	54.420	56.595	70.678	82.487	85.253	87.424
15	54.435	58.088	62.247	75.846	86.606	89.009	90.853
16	60.422	64.057	68.141	81.011	90.486	92.471	93.948
17	66.682	70.420	74.349	86.173	94.054	95.554	96.617
18	73.972	77.363	81.023	91.322	97.165	98.097	98.699
19	82.353	85.413	88.587	96.418	99.447	99.730	99.867

Sample Size = 20							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.127	0.256	0.525	3.406	10.875	13.911	16.843
2	1.235	1.807	2.691	8.251	18.096	21.611	24.873
3	3.207	4.217	5.642	13.147	24.477	28.262	31.698
4	5.733	7.135	9.021	18.055	30.419	34.366	37.893
5	8.657	10.408	12.693	22.967	36.066	40.103	43.661
6	11.893	13.955	16.587	27.880	41.489	45.558	49.105
7	15.391	17.731	20.666	32.795	46.727	50.782	54.279
8	19.119	21.707	24.906	37.711	51.803	55.803	59.219
9	23.058	25.865	29.293	42.626	56.733	60.642	63.946
10	27.196	30.195	33.817	47.542	61.525	65.307	68.472
11	31.528	34.693	38.475	52.458	66.183	69.805	72.804
12	36.054	39.358	43.267	57.374	70.707	74.135	76.942
13	40.781	44.197	48.197	62.289	75.094	78.293	80.881
14	45.721	49.218	53.273	67.205	79.334	82.269	84.609
15	50.895	54.442	58.511	72.120	83.413	86.045	88.107
16	56.339	59.897	63.934	77.033	87.307	89.592	91.343
17	62.107	65.634	69.581	81.945	90.979	92.865	94.267
18	68.302	71.738	75.523	86.853	94.358	95.783	96.793
19	75.127	78.389	81.904	91.749	97.309	98.193	98.765
20	83.157	86.089	89.125	96.594	99.475	99.744	99.873

Sample Size = 21							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.120	0.244	0.500	3.247	10.385	13.295	16.110
2	1.175	1.719	2.562	7.864	17.294	20.673	23.816
3	3.049	4.010	5.367	12.531	23.405	27.055	30.377
4	5.446	6.781	8.577	17.209	29.102	32.921	36.342
5	8.218	9.884	12.062	21.891	34.522	38.441	41.907
6	11.281	13.245	15.755	26.574	39.733	43.698	47.166
7	14.588	16.818	19.619	31.258	44.771	48.739	52.175
8	18.107	20.575	23.632	35.943	49.661	53.594	56.968
9	21.820	24.499	27.779	40.629	54.416	58.280	61.565
10	25.713	28.580	32.051	45.314	59.046	62.810	65.979
11	29.781	32.811	36.443	50.000	63.557	67.189	70.219
12	34.021	37.190	40.954	54.686	67.949	71.420	74.287
13	38.435	41.720	45.584	59.371	72.221	75.501	78.180
14	43.032	46.406	50.339	64.057	76.368	79.425	81.893
15	47.825	51.261	55.229	68.742	80.381	83.182	85.412
16	52.834	56.302	60.267	73.426	84.245	86.755	88.719
17	58.093	61.559	65.478	78.109	87.938	90.116	91.782
18	63.658	67.079	70.898	82.791	91.423	93.219	94.554
19	69.623	72.945	76.595	87.469	94.633	95.990	96.951
20	76.184	79.327	82.706	92.136	97.438	98.281	98.825
21	83.890	86.705	89.615	96.753	99.500	99.756	99.880

Sample Size = 22							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.115	0.233	0.478	3.102	9.937	12.731	15.437
2	1.121	1.640	2.444	7.512	16.559	19.812	22.844
3	2.906	3.822	5.117	11.970	22.422	25.947	29.161
4	5.187	6.460	8.175	16.439	27.894	31.591	34.912
5	7.821	9.411	11.490	20.911	33.104	36.909	40.285
6	10.729	12.603	15.002	25.384	38.117	41.980	45.370
7	13.865	15.994	18.674	29.859	42.970	46.849	50.222
8	17.198	19.556	22.483	34.334	47.684	51.546	54.872
9	29.709	23.272	26.416	38.810	52.275	56.087	59.342
10	24.386	27.131	30.463	43.286	56.752	60.484	63.645
11	28.221	31.126	34.619	47.762	61.119	64.746	67.790
12	32.210	35.254	38.881	52.238	65.381	68.874	71.779
13	36.355	39.516	43.248	56.714	69.537	72.869	75.614
14	40.658	43.913	47.725	61.190	73.584	76.728	79.291
15	45.128	48.454	52.316	65.666	77.517	80.444	82.802
16	49.778	53.151	57.030	70.141	81.326	84.006	86.135
17	54.630	58.020	61.883	74.616	84.998	87.397	89.271
18	59.715	63.091	66.896	79.089	88.510	90.589	92.179
19	65.088	68.409	72.106	83.561	91.825	93.540	94.813
20	70.839	74.053	77.578	88.030	94.883	96.178	97.094
21	77.156	80.188	83.441	92.488	97.556	98.360	98.879
22	84.563	87.269	90.063	96.898	99.522	99.767	99.885

Sample Size = 23							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.110	0.223	0.457	2.969	9.526	12.212	14.819
2	1.071	1.567	2.337	7.191	15.884	19.020	21.949
3	2.775	3.652	4.890	11.458	21.519	24.925	28.038
4	4.951	6.168	7.808	15.734	26.781	30.364	33.589
5	7.460	8.981	10.971	20.015	31.797	35.493	38.781
6	10.229	12.021	14.318	24.297	36.626	40.390	43.703
7	13.210	15.248	17.816	28.580	41.305	45.098	48.405
8	16.376	18.634	21.442	32.863	45.856	49.644	52.919
9	19.708	22.164	25.182	37.147	50.291	54.046	57.226
10	23.191	25.824	29.027	41.431	54.622	58.315	61.458
11	26.820	29.609	32.971	45.716	58.853	62.461	65.505
12	30.588	33.515	37.012	50.000	62.988	66.485	69.412
13	34.495	37.539	41.147	54.284	67.029	70.391	73.180
14	38.542	41.685	45.378	58.569	70.973	74.176	76.809
15	42.734	45.954	49.709	62.853	74.818	77.836	80.292
16	47.081	50.356	54.144	67.137	78.558	81.366	83.624
17	51.595	54.902	58.695	71.420	82.184	84.752	86.790
18	56.297	59.610	63.374	75.703	85.682	87.979	89.771
19	61.219	64.507	68.203	79.985	89.029	91.019	92.540
20	66.411	69.636	73.219	84.266	92.192	93.832	95.049
21	71.962	75.075	78.481	88.542	95.110	96.348	97.225
22	78.051	80.980	84.116	92.809	97.663	98.433	98.929
23	85.151	87.788	90.474	97.031	99.543	99.777	99.890

Sample Size = 24							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.105	0.213	0.438	2.847	9.148	11.735	14.247
2	1.026	1.501	2.238	6.895	15.262	18.289	21.120
3	2.656	3.495	4.682	10.987	20.685	23.980	26.997
4	4.735	5.901	7.473	15.088	25.754	29.227	32.361
5	7.132	8.589	10.497	19.192	30.588	34.181	37.384
6	9.773	11.491	13.694	23.299	35.246	38.914	42.151
7	12.615	14.569	17.033	27.406	39.763	43.469	46.711
8	16.630	17.796	20.493	31.513	44.160	47.873	51.095
9	18.799	21.157	24.058	35.621	48.449	52.142	55.322
10	22.110	24.639	27.721	39.729	52.461	56.289	59.406
11	25.553	28.236	31.476	43.837	56.742	60.321	63.357
12	29.124	31.942	35.317	47.946	60.755	64.244	67.179
13	32.821	35.756	39.245	52.054	64.683	68.058	70.876
14	36.643	39.679	43.258	56.163	68.524	71.764	74.447
15	40.594	43.711	47.359	60.271	72.279	75.361	77.890
16	44.678	47.858	51.551	64.379	75.942	78.843	81.201
17	48.905	52.127	55.840	68.487	79.507	82.204	84.370
18	53.289	56.531	60.237	72.594	82.967	85.431	87.385
19	57.849	60.086	64.754	76.701	86.306	88.509	90.227
20	62.616	65.819	69.412	80.808	89.503	91.411	92.868
21	67.639	70.773	74.246	84.912	92.527	94.099	95.265
22	73.003	76.020	79.315	89.013	95.318	96.505	97.344
23	78.880	81.711	84.738	93.105	97.762	98.499	98.974
24	85.753	88.265	90.852	97.153	99.562	99.787	99.895

Sample Size = 25							
Order Number	**2.5**	**5.0**	**10.0**	**50.0**	**90.0**	**95.0**	**97.5**
1	0.101	0.205	0.421	2.735	8.799	11.293	13.719
2	0.984	1.440	2.148	6.623	14.687	17.612	20.352
3	2.547	3.352	4.491	10.553	19.914	23.104	26.031
4	4.538	5.656	7.166	14.492	24.802	28.172	31.219
5	6.831	8.229	10.062	18.435	29.467	32.961	36.083
6	9.356	11.006	13.123	22.379	33.966	37.541	40.704
7	12.072	13.948	16.317	26.324	38.331	41.952	45.129
8	14.950	17.030	19.624	30.270	42.582	46.221	49.388
9	17.972	20.238	23.032	34.215	46.734	50.364	53.500
10	21.125	23.559	26.529	38.161	50.795	54.393	57.479
11	24.402	26.985	30.111	42.108	54.722	58.316	61.335
12	27.797	30.513	33.774	46.054	58.668	62.138	65.072
13	31.306	34.139	37.514	50.000	62.486	65.861	68.694
14	34.928	37.862	41.332	53.946	66.226	69.487	72.203
15	38.665	41.684	45.228	57.892	69.889	73.015	75.598
16	42.521	45.607	49.205	61.839	73.471	76.441	78.875
17	46.500	49.636	53.266	65.785	76.968	79.762	82.028
18	50.612	53.779	57.418	69.730	80.736	82.970	85.050
19	54.871	58.048	61.669	73.676	83.683	86.052	87.928
20	59.296	62.459	66.034	77.621	86.877	88.994	90.644
21	63.917	67.039	70.533	81.565	89.938	91.771	93.169
22	68.781	71.828	75.198	85.508	92.834	94.344	95.462
23	73.969	76.896	80.086	89.447	95.509	96.648	97.453
24	79.648	82.388	85.313	93.377	97.852	98.560	99.016
25	86.281	88.707	92.201	97.265	99.579	99.795	99.899

Appendix 3: 40 Inventive Principles, Engineering Parameters, and Conflict Matrix

40 INVENTIVE PRINCIPLES

1 Segmentation
2 Extraction
3 Local quality
4 Asymmetry
5 Combining
6 Universality
7 Nesting
8 Counterweight
9 Prior counteraction
10 Prior action
11 Cushion in advance
12 Equipotentiality
13 Inversion
14 Spheroidality
15 Dynamicity
16 Partial or overdone action
17 Moving to a new dimension
18 Mechanical vibration
19 Periodic action
20 Continuity of useful action
21 Rushing through
22 Convert harm into benefit
23 Feedback
24 Mediator
25 Self-service
26 Copying
27 An inexpensive short-life object instead of an expensive durable one
28 Replacement of a mechanical system
29 Use a pneumatic or hydraulic construction
30 Flexible film or thin membranes
31 Use of porous materials
32 Changing the color
33 Homogeneity
34 Rejecting and regenerating parts
35 Transformation of physical and chemical states of an object
36 Phase transition

37 Thermal expansion
38 Use strong oxidizers
39 Inert environment
40 Composite materials

INVENTIVE PRINCIPLES ORDERED BY FREQUENCY OF USE

35	Transformation of physical and chemical states of an object
10	Prior action
1	Segmentation
28	Replacement of a mechanical system
2	Extraction
15	Dynamicity
19	Periodic action
18	Mechanical vibration
32	Changing the color
13	Inversion
26	Copying
3	Local quality
27	An inexpensive short-life object instead of an expensive durable one
29	Use a pneumatic or hydraulic construction
34	Rejecting and regenerating parts
16	Partial or overdone action
40	Composite materials
24	Mediator
17	Moving to a new dimension
6	Universality
14	Spheroidality
22	Convert harm into benefit
39	Inert environment
4	Asymmetry
30	Flexible film or thin membranes
37	Thermal expansion
36	Phase transition
25	Self-service
11	Cushion in advance
31	Use of porous materials
38	Use strong oxidizers
8	Counterweight
5	Combining
7	Nesting
21	Rushing through
23	Feedback
12	Equipotentiality
33	Homogeneity
9	Prior counteraction
20	Continuity of useful action

CONTRADICTION TABLE

Feature to Improve	Undesired Result (Conflict)	1 Weight of moving object	2 Weight of nonmoving object	3 Length of moving object	4 Length of nonmoving object	5 Area of moving object	6 Area of nonmoving object	7 Volume of moving object	8 Volume of nonmoving object	9 Speed	10 Force	11 Tension, pressure	12 Shape	13 Stability of object
1	Weight of moving object			15, 8, 29, 34		29, 17, 38, 34		29, 2, 40, 28		2, 8, 15, 38	8, 10, 18, 37	10, 36, 37, 40	10, 14, 35, 40	1, 35, 19, 39
2	Weight of nonmoving object				10, 1, 29, 35		35, 30, 13, 2		5, 35, 14, 2		8, 10, 19, 35	13, 29, 10, 18	13, 10, 29, 14	26, 39, 1, 40
3	Length of moving object	8, 15, 29, 34				15, 17, 4		7, 17, 4, 35		13, 4, 8	17, 10, 4	1, 8, 35	1, 8, 10, 29	1, 8, 15, 34
4	Length of nonmoving object		35, 28, 40, 29				17, 7, 10, 40		35, 8, 2, 14		28, 10	1, 14, 35	13, 14, 15, 7	39, 37, 35
5	Area of moving object	2, 17 29, 4		14, 15, 18, 4				7, 14, 17, 4		29, 30, 4, 34	19, 30, 35, 2	10, 15, 36, 28	5, 34, 29, 4	11, 2, 13, 39
6	Area of nonmoving object		30, 2, 14, 18		26, 7, 9, 39						1, 18, 35, 36	10, 15, 36, 37		2, 38
7	Volume of moving object	2, 26, 29, 40		1, 7, 4, 35		1, 7, 4, 17				29, 4, 38, 34	15, 35, 36, 37	6, 35, 36, 37	1, 15, 29, 4	28, 10, 1, 39
8	Volume of nonmoving object		35, 10, 19, 14	19, 14	35, 8, 2, 14						2, 18, 37	24, 35	7, 2, 35	34, 28, 35, 40
9	Speed	2, 28, 13, 38		13, 14, 8		29, 30, 34		7, 29, 34			13, 28, 15, 19	6, 18, 38, 40	35, 15, 18, 34	28, 33, 1, 18
10	Force	8, 1, 37, 18	18, 13, 1, 28	17, 19, 6, 36	28, 10	19, 10, 15	1, 18, 36, 37	15, 9, 12, 37	2, 36, 18, 37	13, 28, 15, 12		18, 21, 11	10, 35, 40, 34	35, 10, 21

Feature to Improve	Undesired Result (Conflict)	1 Weight of moving object	2 Weight of nonmoving object	3 Length of moving object	4 Length of nonmoving object	5 Area of moving object	6 Area of nonmoving object	7 Volume of moving object	8 Volume of nonmoving object	9 Speed	10 Force	11 Tension, pressure	12 Shape	13 Stability of object
11	Tension, pressure	10, 36, 37, 40	13, 29, 10, 18	35, 10, 36	35, 1, 14, 16	10, 15, 36, 25	10, 15, 35, 37	6, 35, 10	35, 24	6, 35, 36	36, 35, 21		35, 4, 15, 10	35, 33, 2, 40
12	Shape	8, 10, 29, 40	15, 10, 26, 3	29, 34, 5, 4	13, 14, 10, 7	5, 34, 4, 10		14, 4, 15, 22	7, 2, 35	35, 15, 34, 18	35, 10, 37, 40	34, 15, 10, 14		33, 1, 18, 4
13	Stability of object	21, 35, 2, 39	26, 39, 1, 40	13, 15, 1, 28	37	2, 11, 13	39	28, 10, 19, 39	34, 28, 35, 40	33, 15, 28, 18	10, 35, 21, 16	2, 35, 40	22, 1, 18, 4	
14	Strength	1, 8, 40, 15	40, 26, 27, 1	1, 15, 8, 35	15, 14, 28, 26	3, 34, 40, 29	9, 40, 28	10, 15, 14, 7	9, 14, 17, 15	8, 13, 26, 14	10, 18, 3, 14	10, 3, 18, 40	10, 30, 35, 40	13, 17, 35
15	Durability of moving object	19, 5, 34, 31		2, 19, 9		3, 17, 19		10, 2, 19, 30		3, 35, 5	19, 2, 16	19, 3, 27	14, 26, 28, 25	13, 3, 35
16	Durability of nonmoving object		6, 27, 19, 16		1, 10, 35				35, 34, 38					39, 3, 35, 23
17	Temperature	36, 22, 6, 38	22, 35, 32	15, 19, 9	15, 19, 9	3, 35, 39, 18	35, 38	34, 39, 40, 18	35, 6, 4	2, 28, 36, 30	35, 10, 3, 21	35, 39, 19, 2	14, 22, 19, 32	1, 35, 32
18	Brightness	19, 1, 32	2, 35, 32			19, 32, 26								
19	Energy spent by moving object	12, 18, 28, 31		12, 28		15, 19, 25		35, 13, 18		8, 15, 35	16, 26, 21, 2	23, 14, 25	12, 2, 29	19, 13, 17, 24
20	Energy spent by nonmoving object		19, 9, 6, 27								36, 37			27, 4, 29, 19

CONTRADICTION TABLE (Continued)

Feature to Improve	Undesired Result (Conflict)	14 Strength	15 Durability of moving object	16 Durability of nonmoving object	17 Temperature	18 Brightness	19 Energy spent by moving object	20 Energy spent by nonmoving object	21 Power	22 Water of energy	23 Water of substance	24 Loss of information	25 Waste of time	26 Amount of substance
1	Weight of moving object	28, 27, 18, 40	5, 34, 31, 35		6, 20, 4, 38	19, 1, 32	35, 12, 34, 31		12, 36, 18, 31	6, 2, 34, 19	5, 35, 3, 31	10, 24, 35	10, 35, 20, 28	3, 26, 18, 31
2	Weight of nonmoving object	28, 2, 10, 27		2, 27, 19, 6	28, 19, 32, 22	19, 32, 35		18, 19, 28, 1	15, 19, 18, 22	18, 19, 28, 15	5, 8, 13, 30	10, 15, 35	10, 20, 35, 26	19, 6, 18, 26
3	Length of moving object	8, 35, 29, 34	19		10, 15, 19	32	8, 35, 24		1, 35	7, 2, 35, 39	4, 29, 23, 10	1, 24	15, 2, 29	29, 35
4	Length of nonmoving object	15, 14, 28, 26		1, 40, 35	3, 35, 38, 18	3, 25			12, 8	6, 28	10, 28, 24, 35	24, 26	30, 29, 14	
5	Area of moving object	3, 15, 40, 14	6, 3		2, 15, 16	15, 32, 19, 13	19, 32		19, 10, 32, 18	15, 17, 30, 26	10, 35, 2, 39	30, 26	26, 4	29, 30, 6, 13
6	Area of nonmoving object	40		2, 10, 19, 30	35, 39, 38				17, 32	17, 7, 30	10, 14, 18, 39	30, 16	10, 35, 4, 18	2, 18, 40, 4
7	Volume of moving object	9, 14, 15, 7	6, 35, 4		34, 39, 10, 18	2, 13, 10	35		35, 6, 13, 18	7, 15, 13, 16	36, 39, 34, 10	2, 22	2, 6, 34, 10	29, 30, 7
8	Volume of nonmoving object	9, 14, 17, 15		35, 34, 38	35, 6, 4				30, 6		10, 39, 35, 34		35, 16, 32, 18	35, 3
9	Speed	8, 3, 26, 14	3, 19, 35, 5		28, 30, 36, 2	10, 13, 19	8, 15, 35, 38		19, 35, 38, 2	14, 20, 19, 35	10, 13, 28, 38	13, 26		18, 19, 29, 38

Feature to Improve		14 Strength	15 Durability of moving object	16 Durability of nonmoving object	17 Temperature	18 Brightness	19 Energy spent by moving object	20 Energy spent by nonmoving object	21 Power	22 Water of energy	23 Water of substance	24 Loss of information	25 Waste of time	26 Amount of substance
	Undesired Result (Conflict)													
10	Force	35, 10, 14, 27	19, 2		35, 10, 24		19, 17, 10	1, 16, 36, 37	19, 35, 18, 37	14, 15	8, 35, 40, 5		10, 37, 36	14, 29, 18, 36
11	Tension, pressure	9, 18, 3, 40	19, 3, 27		35, 39, 19, 2		14, 24, 10, 37		10, 35, 14	2, 36, 25	10, 36, 3, 37		37, 36, 4	10, 14, 36
12	Shape	30, 14, 10, 40	14, 26, 9, 25		22, 14, 19, 32	13, 15, 32	2, 6, 34, 14		4, 6, 2	14	35, 29, 3, 5		14, 10, 34, 17	36, 22
13	Stability of object	17, 9, 15	13, 27, 10, 35	39, 3, 35, 23	35, 1, 32	32, 3, 27, 15	13, 19	27, 4, 29, 18	32, 35, 27, 31	14, 2, 39, 6	2, 14 30, 40		35, 27	15, 32, 35
14	Strength		27, 3, 26		30, 10, 40	35, 19	19, 35, 10	35	10, 26, 35, 28	35	35, 28, 31, 40		29, 3, 28, 10	29, 10, 27
15	Durability of moving object	27, 3, 10			19, 35, 39	2, 19, 4, 35	28, 6, 35, 18		19, 10, 35, 38		28, 27, 3, 18	10	20, 10, 28, 18	3, 35, 10, 40
16	Durability of nonmoving object				19, 18, 36, 40				16		27, 16, 18, 38	10	28, 20, 10, 16	3, 35, 31
17	Temperature	10, 30, 22, 40	19, 13, 39	19, 18, 36, 40		32, 30, 21, 16	19, 15, 3, 17		2, 14, 17, 25	21, 17, 35, 38	21, 36, 29, 31		35, 28, 21, 18	3, 17, 30, 39
18	Brightness	35, 19	2, 19, 6		32, 35, 19		32, 1, 19	32, 35, 1, 15	32	19, 16, 1, 6	13, 1	1, 6	19, 1, 26, 17	1, 19
19	Energy spent by moving object	5, 19, 9, 35	28, 35, 6, 18		19, 24, 3, 14	2, 15, 19			6, 19, 37, 18	12, 22, 15, 24	35, 24, 18, 5		35, 38, 19, 18	34, 23, 16, 18

Feature to Improve	Undesired Result (Conflict)	14 Strength	15 Durability of moving object	16 Durability of nonmoving object	17 Temperature	18 Brightness	19 Energy spent by moving object	20 Energy spent by nonmoving object	21 Power	22 Water of energy	23 Water of substance	24 Loss of information	25 Waste of time	26 Amount of substance
20	Energy spent by nonmoving object	35				19, 2, 35, 32					28, 27, 18, 31			3, 35, 31

CONTRADICTION TABLE (Continued)

Feature to Improve	Undesired Result (Conflict)	27 Reliability	28 Accuracy of measurement	29 Accuracy of manufacturing	30 Harmful factors acting on object	31 Harmful side effects	32 Manufacturability	33 Convenience of use	34 Reparability	35 Adaptability	36 Complexity of device	37 Complexity of control	38 Level of automation	39 Productivity
1	Weight of moving object	3, 11, 1, 27	28, 27, 35, 26	28, 35, 26, 18	22, 21, 18, 27	22, 35, 31, 39	27, 28, 1, 36	35, 3, 2, 24	2, 27, 28, 11	29, 5, 15, 8	26, 30, 36, 34	28, 29, 26, 32	26, 35, 18, 19	35, 3, 24, 37
2	Weight of nonmoving object	10, 28, 8, 3	18, 26, 28	10, 1, 35, 17	2, 19, 22, 37	35, 22, 1, 39	28, 1, 9	6, 13, 1, 32	2, 27, 28, 11	19, 15, 29	1, 10, 26, 39	25, 28, 17, 15	2, 26, 35	1, 28, 15, 35
3	Length of moving object	10, 14, 29, 40	28, 32, 4	10, 28, 29, 37	1, 15, 17, 24	17, 15	1, 29, 17	15, 29, 35, 4	1, 28, 10	14, 15, 1, 16	1, 19, 26, 24	35, 1, 26, 24	17, 24, 26, 16	14, 4, 28, 29
4	Length of nonmoving object	15, 29, 28	32, 28, 3	2, 32, 10	1, 18		15, 17, 27	2, 25	3	1, 35	1, 26	26		30, 14, 7, 26
5	Area of moving object	29, 9	26, 28, 32, 3	2, 32	22, 33, 28, 1	17, 2, 18, 39	13, 1, 26, 24	15, 17, 13, 16	15, 13, 10, 1	15, 30	14, 1, 13	2, 36, 26, 18	14, 30, 28, 23	10, 26, 34, 2

Feature to Improve	Undesired Result (Conflict)	27 Reliability	28 Accuracy of measurement	29 Accuracy of manufacturing	30 Harmful factors acting on object	31 Harmful side effects	32 Manufacturability	33 Convenience of use	34 Reparability	35 Adaptability	36 Complexity of device	37 Complexity of control	38 Level of automation	39 Productivity
6	Area of nonmoving object	32, 35, 40, 4	26, 28, 32, 3	2, 29, 18, 36	27, 2, 39, 35	22, 1, 40	40, 16	16, 4	16	15, 16	1, 18, 36	2, 35, 30, 18	23	10, 15, 17, 7
7	Volume of moving object	14, 1, 40, 11	25, 26, 28	25, 28, 2, 16	22, 21, 27, 35	17, 2, 40, 1	29, 1, 40	15, 13, 30, 12	10	15, 29	26, 1	29, 26, 4	35, 34, 16, 24	10, 6, 2, 34
8	Volume of nonmoving object	2, 35, 16		35, 10, 25	34, 39, 19, 27	30, 18, 35, 4	35		1		1, 31	2, 17, 26		35, 37, 10, 2
9	Speed	11, 35, 27, 28	28, 32, 1, 24	10, 28, 32, 25	1, 28, 35, 23	2, 24, 35, 21	35, 13, 8, 1	32, 28, 13, 12	34, 2, 28, 27	15, 10, 26	10, 28, 4, 34	3, 34, 27, 16	10, 18	
10	Force	3, 35, 13, 21	35, 10, 23, 24	28, 29, 37, 36	1, 35, 40, 18	13, 3, 36, 24	15, 37, 18, 1	1, 28, 3, 25	15, 1, 11	15, 17, 18, 20	26, 35, 10, 18	36, 37, 10, 19	2, 35	3, 28, 35, 37
11	Tension, pressure	10, 13, 19, 35	6, 28, 25	3, 35	22, 2, 37	2, 33, 27, 18	1, 35, 16	11	2	35	19, 1, 35	2, 36, 37	35, 24	10, 14, 35, 37
12	Shape	10, 40, 16	28, 32, 1	32, 30, 40	22, 1, 2, 35	35, 1	1, 32, 17, 28	32, 15, 26	2, 13, 1	1, 15, 29	16, 29, 1, 28	15, 13, 39	15, 1, 32	17, 26, 34, 10
13	Stability of object		13	18	35, 24, 30, 18	35, 40, 27, 39	35, 19	32, 35, 30	2, 35, 10, 16	35, 30, 34, 2	2, 35, 22, 26	35, 22, 39, 23	1, 8, 35	23, 35, 40, 3
14	Strength	11, 3	3, 27, 16	3, 27	18, 35, 37, 1	15, 35, 22, 2	11, 3, 10, 32	32, 40, 28, 2	27, 11, 3	15, 3, 32	2, 13, 28	27, 3, 15, 40	15	29, 35, 10, 14
15	Durability of moving object	11, 2, 13	3	3, 27, 16, 40	22, 15, 33, 28	21, 39, 16, 22	27, 1, 4	12, 27	29, 10, 27	1, 35, 13	10, 4, 29, 15	19, 29, 39, 35	6, 10	35, 17, 14, 19

Feature to Improve	Undesired Result (Conflict)	27 Reliability	28 Accuracy of measurement	29 Accuracy of manufacturing	30 Harmful factors acting on object	31 Harmful side effects	32 Manufacturability	33 Convenience of use	34 Reparability	35 Adaptability	36 Complexity of device	37 Complexity of control	38 Level of automation	39 Productivity
16	Durability of nonmoving object	34, 27, 6, 40	10, 26, 24		17, 1, 40, 33	22	35, 10	1	1	2		25, 34, 6, 35	1	10, 20, 16, 38
17	Temperature	19, 35, 3, 10	32, 19, 24	24	22, 33, 35, 2	22, 35, 2, 24	26, 27	26, 27	4, 10, 16	2, 18, 27	2, 17, 16	3, 27, 35, 31	26, 2, 19, 16	15, 28, 35
18	Brightness		11, 15, 32	3, 32	15, 19	35, 19, 32, 39	19, 35, 28, 26	28, 26, 19	15, 17, 13, 16	15, 1, 1, 19	6, 32, 13	32, 15	2, 26, 10	2, 25, 16
19	Energy spent by moving object	19, 21, 11, 27	3, 1, 32		1, 35, 6, 27	2, 35, 6	28, 26, 30	19, 35	1, 15, 17, 28	15, 17, 13, 16	2, 29, 27, 28	35, 38	32, 2	12, 28, 35
20	Energy spent by nonmoving object	10, 36, 23			10, 2, 22, 37	19, 22, 18	1, 4					19, 35, 16, 25		1, 6

CONTRADICTION TABLE (Continued)

Feature to Improve	Undesired Result (Conflict)	1 Weight of moving object	2 Weight of nonmoving object	3 Length of moving object	4 Length of nonmoving object	5 Area of moving object	6 Area of nonmoving object	7 Volume of moving object	8 Volume of nonmoving object	9 Speed	10 Force	11 Tension, pressure	12 Shape	13 Stability of object
21	Power	8, 36, 38, 31	19, 26, 17, 27	1, 10, 35, 37		19, 38	17, 32, 13, 38	35, 6, 38	30, 6, 25	15, 35, 2	26, 2, 36, 35	22, 10, 35	29, 14, 2, 40	35, 32, 15, 31

Feature to Improve	Undesired Result (Conflict)	1 Weight of moving object	2 Weight of nonmoving object	3 Length of moving object	4 Length of nonmoving object	5 Area of moving object	6 Area of nonmoving object	7 Volume of moving object	8 Volume of nonmoving object	9 Speed	10 Force	11 Tension, pressure	12 Shape	13 Stability of object
22	Waste of energy	15, 6, 19, 28	19, 6, 18, 9	7, 2, 6, 13	6, 38, 7	15, 26, 17, 30	17, 7, 30, 18	7, 18, 23	7	16, 35, 38	36, 38			14, 2, 39, 6
23	Waste of substance	35, 6, 23, 40	35, 6, 22, 32	14, 29, 10, 398	10, 28, 24	35, 2, 10, 31	10, 18, 39, 31	1, 29, 30, 36	3, 39, 18, 31	10, 13, 28, 38	14, 15, 18, 40	3, 36, 37, 10	29, 35, 3, 5	2, 14, 30, 40
24	Loss of information	10, 24, 35	10, 35, 5	1, 26	26	30, 26	30, 16		2, 22	26, 32				
25	Waste of time	10, 20, 37, 35	10, 20, 26, 5	15, 2, 29	30, 24, 14, 5	26, 4, 5, 16	10, 35, 17, 4	2, 5, 34, 10	35, 16, 32, 18		10, 37, 36, 5	37, 36, 4	4, 10, 34, 17	35, 3, 22, 5
26	Amount of substance	35, 6, 18, 31	27, 26, 18, 35	29, 14, 35, 18		15, 14, 29	2, 18, 40, 4	15, 20, 29		35, 29, 34, 28	35, 14, 3	10, 36, 14, 3	35, 14	15, 2, 17, 40
27	Reliability	3, 8, 10, 40	3, 10, 8, 28	15, 9, 14, 4	15, 29, 28, 11	17, 10, 14, 16	32, 35, 40, 4	3, 10, 14, 24	2, 35, 24	21, 35, 11, 28	8, 28, 10, 3	10, 24, 35, 19	35, 1, 16, 11	
28	Accuracy of measurement	32, 35, 26, 28,	28, 35, 25, 26	28, 26, 5, 16	32, 28, 3, 16	26, 28, 32, 3	26, 28, 32, 3	32, 13, 6		28, 13, 32, 24	32, 2	6, 28, 32	6, 28, 32	32, 35, 13
29	Accuracy of manufacturing	28, 32, 13, 18	28, 35, 27, 9	10, 28, 29, 37	2, 32, 10	28, 33, 29, 32	2, 29, 18, 36	32, 28, 2	25, 10, 35	10, 28, 32	28, 19, 34, 36	3, 35	32, 30, 40	30, 18
30	Harmful factors acting on object	22, 21, 27, 39	2, 22, 13, 24	17, 1, 39, 4	1, 18	22, 1, 33, 28	27, 2, 39, 35	22, 23, 37, 35	34, 39, 19, 27	21, 22, 35, 28	13, 35, 39, 18	22, 2, 37	22, 1, 3, 35	35, 24, 30, 18
31	Harmful side effects	19, 22, 15, 39	35, 22, 1, 39	17, 15, 16, 22		17, 2, 18, 39	22, 1, 40	17, 2, 40	30, 18, 35, 4	35, 28, 3, 23	35, 28, 1, 40	2, 33, 27, 18	35, 1	35, 40, 27, 39

	Undesired Result (Conflict)	1 Weight of moving object	2 Weight of nonmoving object	3 Length of moving object	4 Length of nonmoving object	5 Area of moving object	6 Area of nonmoving object	7 Volume of moving object	8 Volume of nonmoving object	9 Speed	10 Force	11 Tension, pressure	12 Shape	13 Stability of object
Feature to Improve														
32	Manufacturability	28, 29, 15, 16	1, 27, 36, 13	1, 29, 13, 17	15, 17, 27	13, 1, 26, 12	16, 40,	13, 29, 1, 40	35,	35, 13, 8, 1	35, 12	35, 19, 1, 37	1, 28, 13, 27	11, 13, 1
33	Convenience of use	25, 2, 13, 15,	6, 13, 1, 25	1, 17, 13, 12		1, 17, 13, 16	18, 16, 15, 39	1, 16, 35, 15	4, 18, 39, 31	18, 13, 34	28, 13, 35	2, 32, 12	15, 34, 29, 28	32, 35, 30
34	Reparability	2, 27, 35, 11	2, 27, 35, 11	1, 28, 10, 25	3, 18, 31	15, 13, 32	16, 25	25, 2, 35, 11	1	34, 9	1, 11, 10	13	1, 13, 2, 4	2, 35
35	Adaptability	1, 6, 15, 8	19, 15, 29, 16	35, 1, 29, 2	1, 35, 16	35, 30, 29, 7	15, 16	15, 35, 29		35, 10, 14	15, 17, 20	35, 16	15, 37, 1, 8	35, 30, 14
36	Complexity of device	26, 30, 34, 36	2, 36, 35, 39	1, 19, 26, 24	26	14, 1, 13, 16	6, 36	34, 25, 6	1, 16	34, 10, 28	26, 16	19, 1, 35	29, 13, 28, 15	2, 22, 17, 19
37	Complexity of control	27, 26, 28, 13	6, 13, 28, 1	16, 17, 26, 24	26	2, 13, 15, 17	2, 39, 30, 16	29, 1, 4, 16	2, 18, 26, 31	3, 4, 16, 35	36, 28, 40, 19	35, 36, 37, 32	27, 13, 1, 39	11, 22, 39, 30
38	Level of automation	28, 26, 18, 35	28, 26, 35, 10	14, 13, 17, 28	23	17, 14, 13		35, 13, 16		28, 10	2, 35	13, 35	15, 32, 1, 13	18, 1
39	Productivity	35, 26, 24, 37	28, 27, 15, 3	18, 4, 28, 38	30, 7, 14, 26	10, 26, 34, 31	10, 35, 17, 7	2, 6, 34, 10	35, 37, 10, 2		28, 15, 10, 36	10, 37, 14	14, 10, 34, 40	35, 3, 22, 39

CONTRADICTION TABLE (Continued)

Feature to Improve	Undesired Result (Conflict)	14 Strength	15 Durability of moving object	16 Durability of nonmoving object	17 Temperature	18 Brightness	19 Energy spent by moving object	20 Energy spent by nonmoving object	21 Power	22 Waste of enerry	23 Waster of substance	24 Loss of information	25 Waste of time	26 Amount of substance
21	Power	26, 10, 28	19, 35, 10, 38	16	2, 14, 17, 25	16, 6, 19	16, 6, 19, 37			10, 35, 38	28, 27, 18, 38	10, 19	35, 20, 10, 6	4, 34, 19
22	Waste of energy	26			19, 38, 7	1, 13, 32, 15			3, 38		35, 27, 2, 37	19, 10	10, 18, 32, 7	7, 18, 25
23	Waste of information	35, 28, 31, 40	28, 27, 3, 18	27, 16, 18, 38	21, 36, 39, 31	1, 6, 13	35, 18, 24, 5	28, 27, 12, 31	28, 27, 18, 38	35, 27, 2, 31			15, 18, 35, 10	6, 3, 10, 24
24	Loss of information		10	10		19			10, 19	10, 19			24, 26, 28, 32	24, 28, 35
25	Waste of time	29, 3, 28, 18	20, 10, 28, 18	28, 20, 10, 16	35, 29, 21, 18	1, 19, 26, 17	35, 38, 19, 18	1	35, 20, 10, 6	10, 5, 18, 32	35, 18, 10, 39	24, 26, 28, 32		35, 38, 18, 16
26	Amount of substance	14, 35, 34, 10	3, 35, 10, 40	3, 35, 31	3, 17, 39		34, 29, 16, 18	3, 35, 31	35	7, 18, 25	6, 3, 10, 24	24, 28, 35	35, 38, 18, 16	
27	Reliability	11, 28,	2, 35, 3, 25	34, 27, 6, 40	3, 35, 10	11, 32, 13	21, 11, 27, 19	36, 23	21, 11, 26, 31	10, 11, 35	10, 35, 29, 39	10, 28,	10, 30, 4	21, 28, 40, 3
28	Accuracy of measurement	28, 6, 32	28, 6, 32	10, 26, 24	6, 19, 28, 24	6, 1, 32	3, 6, 32		3, 6, 32	26, 32, 27	10, 16, 31, 28		24, 34, 28, 32	2, 6, 32
29	Accuracy of manufacturing	3, 27	3, 27, 40		19, 26	3, 32	32, 2		32, 2	13, 32, 2	35, 31, 10, 24		32, 26, 28, 18	32, 30

Feature to Improve	Undesired Result (Conflict)	14 Strength	15 Durability of moving object	16 Durability of nonmoving object	17 Temperature	18 Brightness	19 Energy spent by moving object	20 Energy spent by nonmoving object	21 Power	22 Waste of enerry	23 Waster of substance	24 Loss of information	25 Waste of time	26 Amount of substance
30	Harmful side effects	18, 35, 37, 1	22, 15, 33, 28	17, 1, 40, 33	22, 33, 35, 2	1, 19, 32, 13	1, 24, 6, 27	10, 2, 22, 37	19, 22, 31, 2	21, 22, 35, 2	33, 22, 19, 40	22, 10, 2	35, 18, 34	35, 33, 29, 31
31	Harmful side effects	15, 35, 22, 2	15, 22, 33, 31	21, 39, 16, 22	22, 35, 2, 24	19, 24, 39, 32	2, 35, 6	19, 22, 18	2, 35, 18	21, 35, 2, 22	10, 1, 34	10, 21, 29	1, 22	3, 24, 39, 1
32	Manufacturability	1, 3 10, 32	27, 1, 4	35, 16	27, 26, 18	28, 24, 27, 1	28, 26, 27, 1	1, 4	27, 1, 12, 24	19, 35	15, 34, 33	32, 24, 18, 16	35, 28, 34, 4	35, 23, 1, 24
33	Convenience of use	32, 40, 3, 28	29, 3, 8, 25	1, 16, 25	26, 27, 13	13, 17, 1, 24	1, 13, 24		35, 34, 2, 10	2, 19, 13	28, 32, 2, 24	4, 10, 27, 22	4, 28, 10, 34	12, 35
34	Reparability	11, 1, 2, 9	11, 29, 28, 27	1	4, 10	15, 1, 13	15, 1, 28, 16		15, 10, 32, 2	15, 1, 32, 19	2, 35, 34, 27		32, 1, 10, 25	2, 28, 10, 25
35	Adaptability	35, 3, 32, 6	13, 1, 35	2, 16	27, 2, 3, 35	6, 22, 26, 1	19, 35, 29, 13		19, 1, 29	18, 15, 1	15, 10, 2, 13		35, 28	3, 35, 15
36	Complexity of device	2, 13, 28	10, 4, 28, 15		2, 17, 13	24, 17, 13	27, 2, 29, 28		20, 19, 30, 34	10, 35, 13, 2	35, 10, 28, 29		6, 29	13, 3, 27, 10
37	Complexity of control	27, 3, 15, 28	19, 29, 39, 25	25, 24, 6, 35	3, 27, 35, 16	2, 24, 26	35, 38	19, 35, 16	19, 1, 16, 10	35, 3, 15, 19	1, 13, 10, 24	35, 33, 27, 22	18, 28, 32, 9	3, 27, 29, 18
38	Level of automation	25, 13	6, 9		26, 2, 19	8, 32, 19	2, 32, 13		28, 2, 27	23, 28	35, 10, 18, 5	35, 33	24, 28, 35, 30	35, 13
39	Productivity	29, 28, 10, 18	35, 10, 2, 18	20, 10, 16, 38	35, 21, 28, 10	26, 17, 19, 1	35, 10, 38, 19	1	35, 20, 10	28, 10, 29, 35	28, 10, 35, 23	13, 15, 23		35, 38

CONTRADICTION TABLE (Continued)

		27	28	29	30	31	32	33	34	35	36	37	38	39
Feature to Improve	Undesired Result (Conflict)	Reliability	Accuracy of measurement	Accuracy of manufacturing	Harmful factors acting on object	Harmful side effects	Manufacturability	Convenience of use	Reparability	Adaptability	Complexity of device	Complexity of control	Level of automation	Productivity
21	Power	19, 24, 26, 31	32, 15, 2	32, 2	19, 22, 31, 2	2, 35, 18	26, 10, 34	26, 35, 10	35, 2, 10, 34	19, 17, 34	20, 19, 30, 34	19, 35, 16	28, 2, 17	28, 35, 34
22	Waste of energy	11, 10, 35	32		21, 22, 35, 2	21, 35, 2, 22		35, 22, 1	2, 19		7, 23	35, 3, 15, 23	2	28, 10, 29, 35
23	Waste of substance	10, 29, 39, 35	16, 34, 31, 28	35, 10, 24, 31	33, 22, 30, 40	10, 1, 34, 29	15, 34, 33	32, 28, 2, 24	2, 35, 34, 27	15, 10, 2	35, 10, 28, 24	35, 18, 10, 13	35, 10, 18	28, 35, 10, 23
24	Loss of information	10, 28, 23			22, 10, 1	10, 21, 22	32	27, 22				35, 33	35	13, 23, 15
25	Waste of time	10, 30, 4	24, 34, 28, 32	24, 26, 28, 18	35, 18, 34	35, 22, 18, 39	35, 28, 34, 4	4, 28, 10, 34	32, 1, 10	35, 28	6, 29	18, 28, 32, 10	24, 28, 35, 30	
26	Amount of substance	18, 3, 28, 40	13, 2, 28	33, 30	35, 33, 29, 31	3, 35, 40, 39	29, 1, 35, 27	35, 29, 25, 10	2, 32, 10, 25	15, 3, 29	3, 13, 27, 10	3, 27, 29, 18	8, 35	13, 29, 3, 27
27	Reliability		32, 3, 11, 23	11, 32, 1	27, 35, 2, 40	35, 2, 40, 26		27, 17, 40	1, 11	13, 35, 8, 24	13, 35, 1	27, 40, 28	11, 13, 27	1, 35, 29, 38
28	Accuracy of measurement	5, 11, 1, 23			28, 24, 22, 26	3, 33, 39, 10	6, 35, 25, 18	1, 13, 17, 34	1, 32, 13, 11	13, 35, 2	27, 35, 10, 34	26, 24, 32, 28	28, 2, 10, 34	10, 34, 28, 32
29	Accuracy of manufacturing	11, 32, 1			26, 28, 10, 36	4, 17, 34, 26		1, 32, 35, 23	25, 10		26, 2, 18		26, 28, 18, 23	10, 18, 32, 39
30	Harmful factors acting on object	27, 24, 2, 40	28, 33, 23, 26	26, 28, 10, 18			24, 35, 2	2, 25, 28, 39	35, 10, 2	35, 11, 22, 31	22, 19, 29, 40	22, 19, 29, 40	33, 3, 34	22, 35, 13, 24

Feature to Improve	Undesired Result (Conflict)	27 Reliability	28 Accuracy of measurement	29 Accuracy of manufacturing	30 Harmful factors acting on object	31 Harmful side effects	32 Manufacturability	33 Convenience of use	34 Reparability	35 Adaptability	36 Complexity of device	37 Complexity of control	38 Level of automation	39 Productivity
31	Harmful side effects	24, 2, 40, 39	3, 33, 26	4, 17, 34, 26							19, 1, 31	2, 21, 27, 1	2	22, 35, 18, 39
32	Manufacturability		1, 35, 12, 18		24, 2			2, 5, 13, 16	35, 1, 11, 9	2, 13, 15	27, 26, 1	6, 28, 11, 1	8, 28, 1	35, 1, 10, 28
33	Convenience of use	17, 27, 8, 40	25, 13, 2, 34	1, 32, 35, 23	2, 25, 28, 39		2, 5, 12		12, 26, 1, 32	15, 34, 1, 16	32, 26, 12, 17		1, 34, 12, 3	15, 1, 28
34	Reparability	11, 10, 1, 16	10, 2, 13	25, 10	35, 10, 2, 16		1, 35, 11, 10	1, 12, 26, 15		7, 1, 4, 16	35, 1, 13, 11		34, 35, 7, 13	1, 32, 10
35	Adaptability	35, 13, 8, 24	35, 5, 1, 10		35, 11, 32, 31		1, 13, 31	15, 34, 1, 16	1, 16, 7, 4		15, 29, 37, 28	1	27, 34, 35	35, 28, 6, 37
36	Complexity of device	13, 35, 1	2, 26, 10, 34	26, 24, 32	22, 19, 29, 40	19, 1	27, 26, 1, 13	27, 9, 26, 24	1, 13	29, 15, 28, 37		15, 10, 37, 28	15, 1, 24	12, 17, 28
37	Complexity of control	27, 40, 28, 8	26, 24, 32, 28		22, 19, 29, 28	2, 21	5, 28, 11, 29	2, 5	12, 26	1, 15	15, 10, 37, 28		34, 21	35, 18
38	Level of automation	11, 27, 32	28, 26, 10, 34	28, 26, 18, 23	2, 33	2	1, 26, 13	1, 12, 34, 3	1, 35, 13	27, 4, 1, 35	15, 24, 10	34, 27, 25		5, 12, 35, 26
39	Productivity	1, 35, 10, 38	1, 10, 34, 28	18, 10, 32, 1	22, 35, 13, 24	32, 22, 18, 39	35, 28, 2, 24	1, 28, 7, 19	1, 32, 10, 25	1, 35, 28, 37	12, 17, 28, 24	35, 18, 27, 2	5, 12, 35, 26	

Source: Clarke, D.W. Sr., *TRIZ: Through the Eyes of an American TRIZ Specialist, A Study of Ideality, Contradictions, Resources*, Ideation International, 1997. With permission.

Appendix 4: Glossary

ABET: U.S.-based engineering program accrediting agency.

Accelerated testing: Testing at higher-than-normal stress levels to increase the failure rate and shorten the time to wearout.

Acceptable quality level (AQL): The maximum percent defective that, for the purpose of sampling inspection, can be considered satisfactory for a process average.

Acceptance: Sign-off by the purchaser.

Active redundancy: That redundancy wherein all redundant items are operating simultaneously.

Ambient: Used to denote surrounding, encompassing, or local conditions, usually applied to environments.

Archiving: The process of establishing and maintaining copies of controlled items such that previous items, baselines, and configurations can be reestablished should there be a loss or corruption.

Assessment: The review and auditing of an organization's quality management system to determine that it meets the requirements of the standards, that it is implemented, and that it is effective.

Auditee: An organization to be audited.

Auditor: A person who has the qualifications to perform quality audits.

Axiomatic design: A vector-based approach to improved system design.

Baseline: A definition of configuration status declared at a point in the project life cycle.

Burn-in: The operation of items prior to their end application to stabilize their characteristics and identify early failures.

Calibration: The comparison of a measurement system or device of unverified accuracy to a measurement system or device of known and greater accuracy, to detect and correct any variation from required performance specifications of the measurement system or device.

Certification: The process that seeks to confirm that the appropriate minimum best-practice requirements are included and that the quality management system is put into effect.

Certification body: An organization that sets itself up as a supplier of product or process certification against established specifications or standards.

Change notice: A document approved by the design activity that describes and authorizes the implementation of an engineering change to the product and its approved configuration documentation.

Checksum: The sum of every byte contained in an input/output record used for assuring the integrity of the programmed entry.

Checklist: An aid for the auditor listing areas and topics to be covered by the auditors.

Client: A person or organization requesting an audit.

Code of Federal Regulations (CFR): Federal statutes. Title 21 of this material relates the legal code pertaining to the Food and Drug Administration (FDA).

Compliance audit: An audit where the auditor must investigate the quality system, as put into practice, and the organization's results.

Concept map: A way of describing the elements of a process, using a series of concepts interconnected via labeled propositions (directed arrows) that describe the interrelationship of the concepts.

Conditioning: The exposure of sample units or specimens to a specific environment for a specified period of time to prepare them for subsequent inspection.

Confidence: The probability that may be attached to conclusions reached as a result of application of statistical techniques.
Confidence interval: The numerical range within which an unknown is estimated to be.
Confidence level: The probability that a given statement is correct.
Confidence limits: The extremes of a confidence interval within which the unknown has a designated probability of being included.
Configuration: A collection of items at specified versions for the fulfillment of a particular purpose.
Controlled document: Documents with a defined distribution such that all registered holders of control documents systematically receive any updates to those documents.
Corrective action: All action taken to improve the overall quality management system as a result of identifying deficiencies, inefficiencies, and noncompliances.
Creep: Continuous increase in deformation under constant or decreasing stress.
Critical item: An item within a configuration item that, because of special engineering or logistic considerations, requires an approved specification to establish technical or inventory control.
Cycle: An ON/OFF application of power.
Debugging: A process to detect and remedy inadequacies.
Defect: Any nonconformance of a characteristic with specified requirements.
Degradation: A gradual deterioration in performance.
Delivery: Transfer of a product from the supplier to the purchaser.
Derating: The use of an item in such a way that applied stresses are below rated values.
Design entity: An element of a design that is structurally and functionally distinct from other elements and that is separately named and referenced.
Design review: A formal, documented, comprehensive, and systematic examination of a design to evaluate the design requirements and the capability of the design to meet these requirements and to identify problems and propose solutions.
Design view: A subset of design entity attribute information that is specifically suited to the needs of a software project activity.
Deviation: A specific written authorization, granted prior to manufacture of an item, to depart from a particular requirement(s) of an item's current approved configuration documentation for a specific number of units or a specified period of time.
Device: Any functional system.
Discrete variable: A variable that can take only a finite number of values.
Document: Contains information that is subject to change.
Downtime: The total time during which the system is not in condition to perform its intended function.
Early failure period: An interval immediately following final assembly, during which the failure rate of certain items is relatively high.
Entity attribute: A named characteristic or property of a design entity that provides a statement of fact about the entity.
Environment: The aggregate of all conditions that externally influence the performance of an item.
External audit: An audit performed by a customer or his/her representative at the facility of the supplier to assess the degree of compliance of the quality system with documented requirements.
Extrinsic audit: An audit carried out in a company by a third-party organization or a regulatory authority, to assess its activities against specific requirements.
Fail-safe: The stated condition that the equipment will contain self-checking features that will cause a function to cease in case of failure, malfunction, or drifting out of tolerance.
Failure: The state of inability of an item to perform its required function.
Failure analysis: Subsequent to a failure, the logical, systematic examination of any item, its construction, application, and documentation to identify the failure mode and determine the failure mechanism.

Failure mode: The consequence of the mechanism through which the failure occurs.
Failure rate: The probability of failure per unit of time of the items still operating.
Fatigue: A weakening or deterioration of metal or other material, or of a member, occurring under load, specifically under repeated, cyclic, or continuous loading.
Fault: The immediate cause of a failure.
Fault isolation: The process of determining the location of a fault to the extent necessary to effect repair.
Feasibility study: The study of a proposed item or technique to determine the degree to which it is practicable, advisable, and adaptable for the intended.
Firmware: The combination of a hardware device and computer instructions or computer data that reside as read-only software on the hardware device.
Form: The shape, size, dimensions, mass, weight, and other visual parameters that uniquely characterize an item.
Grade: An indicator or category or rank relating to features or characteristics that cover different sets of needs for products or services intended for the same functional use.
Inherent failure: A failure basically caused by a physical condition or phenomenon internal to the failed item.
Inherent reliability: Reliability potential present in the design.
Inspection: The examination and testing of supplies and services to determine whether they conform to specified requirements.
Installation: Introduction of the product to the purchaser's organization.
Internal audit: An audit carried out within an organization by its own personnel to assess compliance of the quality system to documented requirements.
Item: Any entity whose development is to be tracked.
Maintainability: The measure of the ability of an item to be retained in or restored to a specified condition when maintenance is performed by personnel having specified skill levels, using prescribed procedures and resources, at each prescribed level of maintenance and repair.
Maintenance: The servicing, repair, and care of material or equipment to sustain or restore acceptable operating conditions.
Major noncompliance: Either the nonimplementation, within the quality system of a requirement of ISO 9001, or a breakdown of a key aspect of the system.
Malfunction: Any occurrence of unsatisfactory performance.
Manufacturability: The measure of the design's ability to consistently satisfy product goals, while being profitable.
MAUDE: Manufacturers and users device experience database, maintained by the FDA.
Mean time between failure (MTBF): A basic measure of reliability for repairable items.
Mean time to failure (MTTF): A basic measure of maintainability.
Mean time to repair (MTTR): The sum of repair times divided by the total number of failures, during a particular interval of time, under stated conditions.
Method: A prescribed way of doing things.
Metric: A value obtained by theoretical or empirical means in order to determine the norm for a particular operation.
Minimum life: The time of occurrence of the first failure of a device.
Minor noncompliance: A single and occasional instance of a failure to comply with the quality system.
Module: A replaceable combination of assemblies, subassemblies, and parts common to one mounting.
Noncompliance: The nonfulfillment of specified requirements.
Objective evidence: Qualitative or quantitative information, records, or statements of fact pertaining to the quality of an item or service or to the existence and the implementation of a quality system element, which is based on observation, measurement, or test, and which can be verified.

Observation: A record of an observed fact that may or may not be regarded as a noncompliance.

Parameter: A quantity to which the operator may assign arbitrary values, as distinguished from a variable, which can assume only those values that the form of the function makes possible.

Pareto chart: Generally a histogram of labeled problems, arranged in descending order. Occasionally, a cumulative total chart is overlaid.

Parsing: The technique of marking system or subsystem requirements with specified attributes in order to sort the requirements according to one or more of the attributes.

Performance standards: Published instructions and requirements setting forth the procedures, methods, and techniques for measuring the designed performance of equipment or systems in terms of the main number of essential technical measurements required for a specified operational capacity.

Phase: A defined segment of work.

Population: The total collection of units being considered.

Precision: The degree to which repeated observations of a class of measurements conform to themselves.

Predicted: That which is expected at some future time, postulated on analysis of past experience and tests.

Preventive maintenance: All actions performed in an attempt to retain an item in specified condition by providing systematic inspection, detection, and prevention of incipient failures.

Probability: A measure of the likelihood of any particular event occurring.

Probability distribution: A mathematical model that represents the probabilities for all of the possible values a given discrete random variable may take.

Procedures: Documents that explain the responsibilities and authorities related to particular tasks, indicate the methods and tools to be used, and may include copies of, or reference to, software facilities or paper forms.

Product: Operating system or application software including associated documentation, specifications, user guides, and so forth.

Program: The program of events during an audit.

Prototype: A model suitable for use in complete evaluation of form, design, and performance.

Purchaser: The recipient of products or services delivered by the supplier.

Qualification: The entire process by which products are obtained from manufacturers or distributors, examined and tested, and then identified on a qualified products list.

Quality: The totality of features or characteristics of a product or service that bear on its ability to satisfy stated or implied needs.

Quality assurance: All those planned and systematic actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality.

Quality audit: A systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

Quality control: The operational techniques and activities that are used to fulfill requirements for quality.

Quality function deployment: A customer-oriented graphical methodology for the determination of best approaches for product function and deployment planning.

Quality management: That aspect of the overall management function that determines and implements quality policy.

A technique covering quality assurance and quality control aimed at ensuring defect-free products.

Quality policy: The overall intention and direction of an organization regarding quality as formally expressed by top management.

Management's declared targets and approach to the achievement of quality.

Quality system: The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

Record: Provides objective evidence that the quality system has been effectively implemented. A piece of evidence that is *not* subject to change.

Redundancy: Duplication, or the use of more than one means of performing a function in order to prevent an overall failure in the event that all but one of the means fail.

Regression analysis: The fitting of a curve or equation to data in order to define the functional relationship between two or more correlated variables.

Reliability: The probability that a device will perform a required function, under specified conditions, for a specified period of time.

Reliability goal: The desired reliability for the device.

Reliability growth: The improvement in a reliability parameter caused by the successful correction of deficiencies in item design or manufacture.

Repair: All actions performed as a result of failure, to restore an item to a specified condition.

Review: An evaluation of software elements or project status to ascertain discrepancies from planned results and to recommend improvement.

Review meeting: A meeting at which a work product or a set of work products is presented to project personnel, managers, users, customers, or other interested parties for comment or approval.

Revision: Any change to an original document that requires the revision level to be advanced.

Risk: The probability of making an incorrect decision.

Robust design: A design technique, originated by Taguchi, that seeks to improve processes by improving the fundamental operations of the device/process.

Safety factor: The margin of safety designed into the application of an item to ensure that it will function properly.

Schedule: The dates on which the audit is planned to happen.

Screening: A process of inspecting items to remove those that are unsatisfactory or those likely to exhibit early failure.

Service-level agreement: Defines the service to be provided and the parameters within which the service provider is contracted to service.

Shelf life: The length of time an item can be stored under specified conditions and still meet specified requirements.

Simulation: A set of test conditions designed to duplicate field operating and usage environments as closely as possible.

Single point failure: The failure of an item that would result in failure of the system and is not compensated for by redundancy or alternative operational procedures.

Six Sigma: A specialized business process improvement process.

Skunk works: A term originating in the defense industry, currently meant to indicate a self-sufficient design and development group.

Software: A combination of associated computer instructions and computer data definitions required to enable the computer hardware to perform computational or control functions.

Software design description: A representation of a software system created to facilitate analysis, planning, implementation, and decision making.
A blueprint or model of the software system.

Source code: The code in which a software program is prepared.

Specification: A document that describes the essential technical requirements for items, materials, or services.

Standards: Documents that state very specific requirements in terms of appearance, formal and exact methods to be followed in all relevant cases.

Standard deviation: A statistical measure of dispersion in a distribution.

Standby redundancy: That redundancy wherein the alternative means of performing the function is not operating until it is activated upon failure of the primary means of performing the function.

Subcontractor: The organization that provides products or services to the supplier.

Supplier: The organization responsible for replication and issue of product.
The organization to which the requirements of the relevant parts of an ISO 9000 standard apply.

System: A group of equipment, including any required operator functions, which are integrated to perform a related operation.

System compatibility: The ability of the equipment within a system to work together to perform the intended mission of the system.

Testing: The process of executing hardware or software to find errors.
A procedure or action taken to determine, under real or simulated conditions, the capabilities, limitations, characteristics, effectiveness, reliability, and suitability of a material, device, or method.

Tolerance: The total permissible deviation of a measurement from a designated value.

Tool: The mechanization of the method or procedure.

Total quality: A business philosophy involving everyone for continuously improving an organization's performance.

Traceability: The ability to track requirements from the original specification to code and test.

Trade-off: The lessening of some desirable factor(s) in exchange for an increase in one or more other factors to maximize a system's effectiveness.

Useful life period: The period of equipment life following the infant mortality period, during which the equipment failure rate remains constant.

Validation: The process of evaluating a product to ensure compliance with specified and implied requirements.

Variable: A quantity that may assume a number of values.

Variance: A statistical measure of the dispersion in a distribution.

Variant: An instance of an item created to satisfy a particular requirement.

Verification: The process of evaluating the products of a given phase to ensure correctness and consistency with respect to the products and standards provided as input to that phase.

Version: An instance of an item or variant created at a particular time.

Wear-out: The process that results in an increase in the failure rate or probability of failure with increasing number of life units.

Wear-out failure period: The period of equipment life following the normal failure period, during which the equipment failure rate increases above the normal rate.

Work instructions: Documents that describe how to perform specific tasks and are generally only required for complex tasks that cannot be adequately described by a single sentence or paragraph with a procedure.

Worst-case analysis: A type of circuit analysis that determines the worst possible effect on the output parameters by changes in the values of circuit elements. The circuit elements are set at the values within their anticipated ranges that produce the maximum detrimental output changes.

Design of Biomedical Devices and Systems

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711 Third Avenue
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2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

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