Development of FDA-Regulated Medical Products

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Development of FDA-Regulated Medical Products

A Translational Approach

Second Edition

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In loving memory of Emma and James Peters.

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Acronyms and Abbreviations

BLA—Biologics License Application

CBER—Center for Biologics Evaluation and Research

CDC—Centers for Disease Control and Prevention

CDER—Center for Drug Evaluation and Research

CDRH—Center for Devices and Radiological Health

CEA—cost-effectiveness analysis

CER—comparative effectiveness research

CPI—critical path initiative

CRO—contract research organization

FDA FD&C Act—Food, Drug, and Cosmetic Act

FDAMA—Food and Drug Administration Modernization Act

510(k)—Premarket Notification application

FMECA—failure mode effects and criticality analysis

FTA—fault tree analysis

GCP—good clinical practice

GLP—good laboratory practice

GMP—good manufacturing practice

HFE—human factors engineering

ICH—International Conference on Harmonization

IDE—Investigational Device Exemption

IND—Investigational New Drug application

IP—intellectual property

ISO—International Organization for Standardization

MDUFMA—Medical Device User Fee and Modernization Act

NDA—New Drug Application

NIH—National Institutes of Health

NME—new molecular entity

NSF—National Science Foundation

OCP—Office of Combination Products

PDUFA—Prescription Drug User Fee Act

PHS Act—Public Health Service Act

PMA—Premarket Approval

QFD—quality function deployment

QOL—quality of life

SMDA—Safe Medical Devices Act

TQM—total quality management

Preface

The years since the publication of the previous edition of this book have seen profound changes in the actions and attitudes of patients, insurers, manufacturers, and the Food and Drug Administration regarding the streamlining of medical product development and approval. What those years have not seen is a concomitant increase in innovative treatments with profound benefits to patients.

Over the past decade, the path to the development of new drugs, biologics, and medical devices in the United States has become increasingly inefficient, costly, and strewn with formidable obstacles. Despite enormous investments in research by both private and public sources and a surge in scientific and technological advances, new medical products barely trickle into the marketplace. For a variety of reasons, applied sciences necessary for medical product development are not keeping pace with the tremendous advances in basic sciences.

Not surprisingly, industry and academia are under substantial pressure to transform discoveries and innovations from the laboratory into safe and effective medical products to benefit patients and improve health. This evolution—from bench to bedside—has become known as *translational research and development*.

Translating promising discoveries and innovations into useful, marketable medical products demands a robust process to guide nascent products through a tangle of scientific, clinical, regulatory, economic, social, and legal challenges. There are so many human and environmental elements involved in shepherding medical advances from lab to launch that the field of medical product development has been referred to as an ecosystem. The purpose of this book is to help provide a shared foundation from which cross-functional participants in that ecosystem can negotiate the product

development labyrinth and accomplish the goal of providing both groundbreaking and iterative new medical products. This book is intended for anyone in industry, the public sector, or academia—regardless of functional specialty, workplace, or seniority—who is interested in medical product development.

Part I

Unique Challenges in Medical Product Development

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1

Pushing the Pipeline

Translational Research and Product Development

How wonderful that we have met with a paradox. Now we have some hope of making progress.

—Niels Bohr

The U.S. healthcare product pipeline needs major plumbing repair.

There is no lack of innovation or shortage of important scientific discoveries in this country, but our ability to transform scientific advances into new and effective medical products has been disappointing. Despite a steady increase in the amount of money invested in research and development, there is a serious gap in making the transition from the research lab to the patient. Novelty and innovation are the goals of academic and corporate research funding and honors. But to have an impact on healthcare, innovations must be shepherded through challenging stages subject to rigorous Food and Drug Administration (FDA) requirements, as well as through business development–related scrutiny. It is not an easy or intuitively obvious road from lab to launch, and productivity in terms of the introduction of new, innovative drugs, biologics, and medical devices has not kept pace with opportunities or expectations. The pipeline needs a big push.

PRODUCTIVITY GAP

Although the productivity gap certainly exists for biological products and medical devices, as well as prescription drugs, for the sake of simplicity, let us examine U.S. industry expenditure on research and development of pharmaceuticals relative to the number of new, innovative drugs that have been approved by FDA during the same time period. To dissect innovation from elaboration or imitation, only *new molecular entities* (NMEs) will be

examined. The distinction between NMEs and other traditional drugs is summarized below:

- Innovation = *NMEs*, which are defined as active ingredients that have never before been marketed in the United States in any form. This is the category that comprises truly new therapeutic products.
- Elaboration = *Non-NME new drugs*, which include incremental modifications of existing drugs, such as changes in formulation or new indications (additional health conditions for which an existing drug can be prescribed). Although clinical trials are required to gain FDA approval, since the initial discovery and preclinical and clinical safety testing of the active drug component have already been done, the development costs and regulatory review times are usually substantially lower than for NMEs.
- Imitation = *Generic drugs*, which are the same as a brand-name drug in dosage, safety, strength, administration, quality, performance, and intended use. FDA requires specific scientific data on the therapeutic equivalence of generic drugs to the branded drug, but does not require clinical trials. Consequently, development costs are not even in the same league as for NMEs or non-NME new drugs.

According to the U.S. Congressional Budget Office, the pharmaceutical industry is one of the most research-intensive industries in the United States.[1] Pharmaceutical firms invest as much as five times more in research and development (R&D), relative to their sales, than the average U.S. manufacturing firm. Government-funded research institutes and agencies such as National Institutes of Health (NIH), NSF, and the Centers for Disease Control and Prevention (CDC) have ramped up R&D spending. Publicly and privately funded academic R&D activity at universities and hospitals is continuing at a pace commensurate with funding. Despite this, the rate at which U.S. innovators have been able to bring new drugs from the research pipeline into the market has slowed considerably over the past decade.

Figure 1.1 shows the estimated amount of money spent on R&D by the private pharmaceutical sector. In Table 1.1, we see that the number of NME approvals has essentially stagnated. Furthermore, applications for NME approvals are not increasing, and candidate products did not appear to be any more likely to advance to the stage of final FDA review in 2011 than in 2000. Some new therapeutic biological products are considered to be NMEs, and are included here in the discussions of NMEs.

A myriad of explanations can be presented. Blame has been placed on outdated clinical trial models and inefficient regulatory review and

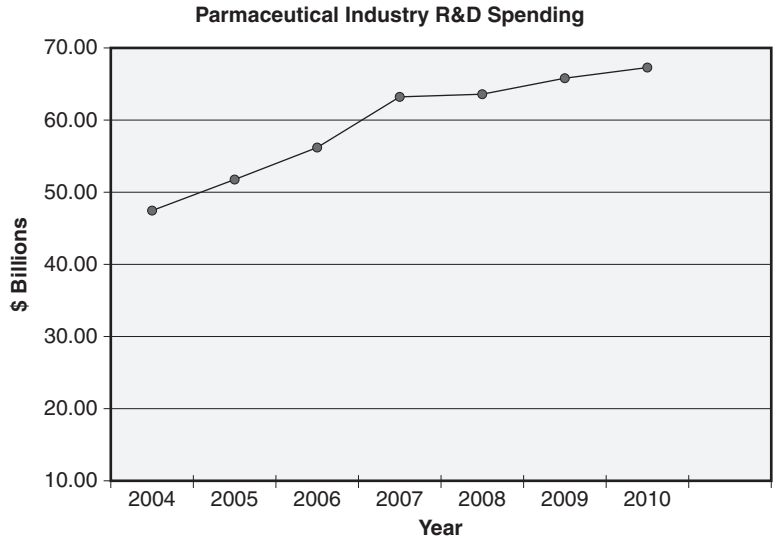

Figure 1.1 Pharmaceutical industry R&D spending.
Source: PhRMA 2011 Industry Profile.

Table 1.1 New molecular entities: applications and approvals.

Calendar year	NME applications filed	NMEs approved
2004	32	36
2005	38	20
2006	26	22
2007	35	18
2008	34	24
2009	37	26
2010	23	21

Source: FDA Center for Drug Evaluation and Research.

approval processes. Costs are often cited as an impediment. Indeed, costs are a significant problem, but if investments are being made with dwindling numbers of deliverables, blame also must be directed to the way the money is being spent. While individual elements do contribute to failure, the most egregious problem lies within the product development process itself.

It is estimated that development of a therapeutic new molecular entity to the point of approval takes up to 15 years (see Figure 1.2). Recent estimates place the cost of developing a commercialized NME at over $1.3 billion (Figure 1.3).[2] The numbers in Figure 1.3 include costs associated with R&D and the costs of failed projects, which are capitalized and time adjusted. These are disheartening figures, and the associated productivity gap has become a concern to industry, academia, FDA and other government agencies, lawmakers, public and private funding sources, and patient advocacy groups. Of course, there are the concerned patients themselves, who hear or read reports on a daily basis about exciting discoveries that hold promise for diagnosis, treatment, cure, or prevention of diseases—but who rarely get to hear about, or benefit from, the availability of any breakthrough products.

Because of the great diversity within medical devices, and because there are different regulatory pathways for various types of devices, estimates of product development time and costs are less readily analyzed, but the overall trend holds true. A recent report says that taking a medium-risk medical device cleared for marketing through the Premarket Notification 510(k) process requires $31 million on average, and that bringing

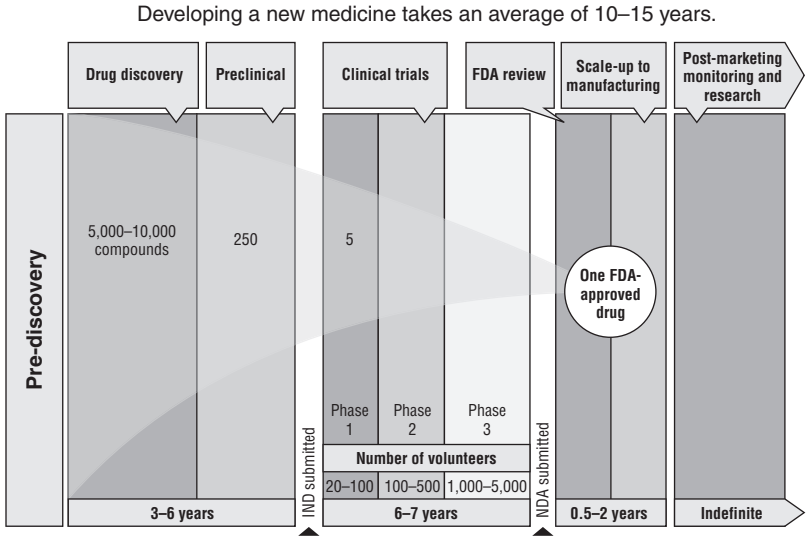

Figure 1.2 Drug development pathway.

Source: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development: Understanding the R&D Process, www.Innovation.org.

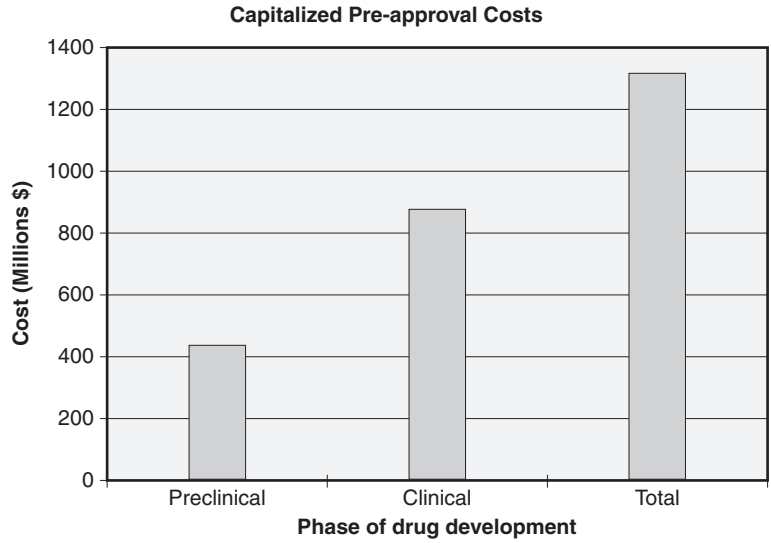

Figure 1.3 Preapproval capitalized cost per approved NME.
Source: DiMasi and Grabowski 2007.

a high-risk device approved for marketing through the more rigorous premarket approval (PMA) process burns up about $94 million.[3] About three-quarters of those costs are related to stages linked to FDA. The devices in the report are likely to be innovative new medical technologies requiring clinical data, rather than simply extensions or products demonstrated to be substantially equivalent to low or intermediate risk devices.

From a regulatory perspective, biologics may function as either drugs—including but not limited to NMEs—or medical devices, and are similarly affected by the productivity gap. Distinctions in drug, medical device, and biologic product categorization and classification are discussed elsewhere in this book.

Translational R&D

Moving a scientific idea, discovery, or design from the research stage, through the product development process, to a viable and marketable medical product can be a formidable challenge. Surmounting the obstacles calls for a revision in attitudes and processes related to medical product development. Enter *translational research*. Translational research—also frequently called *translational science* or *translational development*—refers

to concepts and practices intended to advance scientific discoveries from the lab to the patient. The approach is typically described as "bench to bedside."

As a relatively new and evolving discipline, translational research and development has somewhat different meanings depending on the particular institution or interest group engaged in its applications to medical products or healthcare practices. Examples of these definitions are shown in Figure 1.4. For the purposes of this book, with its focus on the development of marketable prescription drugs, biologics, medical devices, and combinations thereof, the definition of translational research proposed by the Coulter Foundation seems most suitable:

- It is driven primarily by considerations of use and practical applications of the research results, as opposed to basic research, which is driven primarily by a quest for knowledge.
- It envisions the development of a practical solution that addresses a particular clinical problem or unmet clinical need.
- It often envisions as an endpoint the development of a particular product.
- The research results generally include intellectual property that can be protected by patents.
- It involves clinical application as a goal, and therefore requires a transition (a translation) of the research from the research laboratory to the clinic ("bench to bedside").
- It involves commercialization as a goal, and therefore requires a transition (a translation) of the technology (technology transfer) from the academic institution to a commercial entity for final product development, manufacturing, and sales.[4]

In addition to the existence of diverse definitions of translational research, there are other complicating terminology factors. Translational research is sometimes divided into two stages or phases, sometimes into three, and sometimes into four. In the most general sense, the first stage (T1) is the advancement of research laboratory discoveries to clinical studies, and the second (T2) is focused on moving knowledge gained from clinical trials into the community via clinical practice and treatment strategies. However, even among researchers using, for example, a two-stage concept, there is disagreement as to when T1 ends and T2 begins. Sometimes, T1 is considered bench through early clinical trials, and T2 is considered pivotal

Definition: Translational research is the application of discoveries from basic biomedical and behavioral research toward the diagnosis, treatment, or prevention of human disease, with the ultimate goal of improving public health.

Source: National Institutes of Health.

Definition: Translational research—the two-way transfer between work at the laboratory bench and patient care.

Source: Burroughs Wellcome Fund.

Definition: Translational research is research that has some or all of the following characteristics:

- It is driven primarily by considerations of use and practical applications of the research results, as opposed to basic research, which is driven primarily by a quest for knowledge.
- It envisions the development of a practical solution that addresses a particular clinical problem or unmet clinical need.
- It often envisions as an endpoint the development of a particular product.
- The research results generally include intellectual property that can be protected by patents.
- It involves clinical application as a goal, and therefore requires a transition (a translation) of the research from the research laboratory to the clinic ("bench to bedside").
- It involves commercialization as a goal, and therefore requires a transition (a translation) of the technology (technology transfer) from the academic institution to a commercial entity for final product development, manufacturing, and sales.

Source: Coulter Foundation.

Definition: Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality.

Source: National Cancer Institute.

Definition: Translational research includes two areas of translation. One is the process of applying discoveries generated during research in laboratory, and in preclinical studies, to the development of trials and studies in human studies. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community.

Source: Bausell, R. B. 2006. "Translation Research: Introduction to the Special Issue." *Evaluation in the Health Professions* 29 (1): 3–6.

Figure 1.4 Some definitions of translational research.

Definition: Traditional boundaries between basic research, clinical research, and patient-oriented research are yielding to a single, continuous, bidirectional spectrum commonly termed "translational research" or "translational medicine." *Source:* Hörig, E., E. Marincola, and F. M. Marincola. 2005. "Obstacles and Opportunities in Translational Research." *Nature Medicine* 11: 705–8.
Definition: It's the bridge from discovery to delivery. It has a clinical goal or target in mind, which isn't the case for basic research. *Source:* Columbia University Medical Centre.
Definition: Translational research is generally described as the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of disease or injury. . . . It is bidirectional in nature, working from the laboratory to the clinic, and from the clinic back to the laboratory. Translational research is, therefore, an inherently collaborative and interdisciplinary area of research. *Source:* Ontario Neurotrauma Foundation.

Figure 1.4 *Continued.*

clinical trials to approval and beyond; sometimes, T1 is considered bench through completion of clinical trials, and T2 is application of clinical data to real-world use. Further subdivision of translational research into T3 and T4—which involve such things as developing standards of care, population-based clinical effectiveness, comparative costs and outcomes evaluations—is at risk of vague, subjective, and inconsistent definitions.

Furthermore, since the objective begins with research, but requires the involvement of disciplines other than strictly research or science, it would seem that the term *translational product development* more clearly reflects the requirement for a multidisciplinary approach to take a project from the lab to the patients and practitioners. Focusing on "research" or "science" as the nouns to which the adjective "transitional" is applied may not adequately foster the awareness and acceptance of other necessary skills and activities, which will not help to repair the medical product pipeline. It is important, though, that the gestalt of translational research and product development not become overshadowed by semantic differences. The discipline is about transitioning biomedical breakthroughs and inventions into innovative, clinically effective products that improve healthcare. As the field grows and translational concepts of "bench to bedside" continue to be implemented, terminology is likely to become more standardized.

At a minimum, the complex process of shepherding an idea or discovery from bench to bedside involves:

- Scientific discovery related to the pathogenesis of a disease

- Initial scientific assessment of the potential of the discovery to lead to a clinical advance in the diagnosis, treatment, or prevention of a disease
- Initial/prototype development of a candidate drug, biologic, medical device, or combination product
- Proof of concept and optimization of the candidates in preclinical bench testing
- Safety and efficacy testing in in vitro and in vivo preclinical testing
- Application for approval for clinical evaluation
- Clinical trials
- Regulatory submissions and FDA's review of the data to determine the suitability for approval
- Post-market assessment of the new approved product for safety and effectiveness in real-world settings

Additional troublesome steps may include (in no particular order) determining patent position and applying for intellectual property protection; identifying cross-functional product development teams; implementing usability engineering; managing risk; developing and selecting preclinical models that have reasonable correlation with humans for the expected use of the product; designing clinical models with meaningful endpoints; identifying clinical investigators, recruiting patients, and monitoring the clinical trials; establishing an acceptable manufacturing process and facility; holding many meetings with FDA; acquiring funding for all of the above, and then some. It is also a two-way street, with information gained at one step providing feedback to previous steps to allow optimization of the new product design, effectiveness, and appropriate use. Medical product development is clearly an interactive and cooperative process dependent on a wide range of skills.

Valley of Death

According to the NIH, 80 to 90% of research projects fail before they ever get tested on humans, and industry statistics suggest that the number is far higher. The failure-plagued period of development from scientific discovery to initial clinical evaluations on humans has come to be known as the "valley of death."[5,6]

Scientific discoveries typically occur in academic settings. Few, if any, academic researchers have the financial resources or experience to conduct

all of the studies needed to develop a new healthcare product. It takes many years and many millions of dollars to traverse the preclinical development stage. Overall capitalized time-adjusted costs for preclinical development of an approved NME have been estimated at $439 million, including discovery and failed project costs. For 510(k) devices, it is in the range of $7 million, and for PMA devices, $19 million.

For economic and other reasons, investors and industry have been reluctant to commit the funding required to advance to and through clinical trials without substantial validation of the potential clinical utility of a discovery. But those involved in the discovery phase often don't have the large sums of money to do additional testing to satisfy investors. No money, no testing, no money. Small start-up research companies face the same dilemma. So, scientists publish, apply for new grants, and go on with basic research, and, consequently, potentially important treatments and cures are lost.

The NIH has taken a lead role in drawing attention to the preclinical valley of death and to the objectives of translational research. The agency also has programs to help fund translational research, as well as to provide scientific resources to translational efforts. Other public funding, at the federal and state levels, and from private and industry sources, is becoming available to help in the transition of scientific innovation from bench to bedside (see Figure 1.5).

- Federal
  - National Institutes of Health
  - Other federal (for example, National Science Foundation, Department of Defense, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Small Business Administration)
- Industry: pharmaceutical, medical device, biotechnology
- Private research foundations
- Private charities and advocacy groups
- State and local government
- Venture capital and other investment groups
- Academic institutions

Figure 1.5 Sources of funding and support for translational research and development.

Translational Research and FDA Initiatives

Critical Path Initiative

After much time on the receiving end of criticism for its part in the new product stagnation problem, FDA is joining the movement to accelerate the development of innovative medical products. In 2004, FDA instituted the *Critical Path Initiative* (CPI), described as FDA's national strategy to drive innovation in scientific processes through which medical products are developed, evaluated, and manufactured. The original focus was on drug development, but quickly expanded to embrace biologics and medical devices, and it now applies to all medical products regulated by FDA.

Concurrent with the launch of CPI, FDA released a landmark report presenting the agency's analysis of the reasons for the widening gap between scientific discoveries that have unlocked the potential to prevent and cure some of today's biggest medical challenges and their translation into innovative medical treatments.[7] In that report, FDA explained that the goal of CPI is more-efficient medical product development and evaluation, as well as improved quality, safety, and effectiveness of products regulated by FDA. The report concluded that collective action involving industry, academia, and government agencies is needed to modernize scientific and technical tools, as well as harness information technology to evaluate and predict the safety, effectiveness, and manufacturability of medical products.

Two years after the launch of CPI, the FDA commissioner announced the release of a follow-up document.[8] Created with broad contribution from the public, this publication eloquently described specific topics where the sciences of product development, from FDA's perspective, had the greatest need for early attention and improvement. They are:

Topic 1: Better evaluation tools—developing new biomarkers and disease models

Topic 2: Streamlining clinical trials

Topic 3: Harnessing bioinformatics

Topic 4: Moving manufacturing into the twenty-first century

Topic 5: Developing products to address urgent public health needs

Topic 6: At-risk populations—pediatrics

FDA has identified scientific and technical dimensions along the critical path (Table 1.2). In describing the dimensional concept, FDA explains

Table 1.2 Three dimensions of the critical path.

Dimension	Definition	Examples of activities
Assessing safety	Show that product is adequately safe for each stage of development	• Preclinical: show that product is safe enough for early human testing • Eliminate products with safety problems early • Clinical: show that product is safe enough for commercial distribution
Demonstrating medical utility	Show that the product benefits people	• Preclinical: Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness • Clinical: show effectiveness in people
Industrialization	Go from lab concept or prototype to a manufacturable product	• Design a high-quality product – Physical design – Characterization – Specifications • Develop mass production capacity – Manufacturing scale-up – Quality control

Source: FDA. 2004. "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products."

that—whether working with devices, drugs, or biologics—medical product developers must negotiate three crucial, interdependent scientific/technical dimensions on the critical path from scientific innovation to commercial product: assessing safety, demonstrating medical utility, and industrialization. The vast majority of medical product development costs are attributable to these three dimensions.

Driving Biomedical Innovation

In late 2011, FDA outlined steps to spur biomedical innovation, addressing concerns about sustainability of the medical product development pipeline

which, as we have seen, is slowing down despite record investments in R&D. The plan seeks to implement initiatives to facilitate translation of scientific opportunities into safe and effective medical products by focusing on:

- Rebuilding FDA's small business outreach services
- Building the infrastructure to drive and support personalized medicine
- Creating a rapid drug development pathway for important targeted therapies
- Harnessing the potential of data mining and information sharing while protecting patient privacy
- Improving consistency and clarity in the medical device review process
- Training the next generation of innovators
- Streamlining and reforming FDA regulations[9]

There are indications that the number of FDA approvals of innovative new products began to increase in 2011, and that the review times may be improving. This might represent statistical noise, but there is optimism that it is a real trend arising from the positive influence of translational research and development measures.

As the primary centers for basic research, universities have begun to take note of the importance of translational techniques and the multidisciplinary requirements for medical product development. Many schools have courses, programs, or departments devoted to fields such as regulatory affairs, clinical trial design, medical device bioengineering, drug development, and translational research (Figure 1.6). It is also vital that university technology transfer offices that license new technologies from the school to venture capital groups (frequently for early-stage funding), or to private industry (often at stages beyond proof-of-concept), as well as the funding entities themselves, attain an adequate comfort level with translational research and product development techniques. Clearly, a thorough understanding of the requirements and the processes involved in the translation of scientific and technical discoveries into clinically relevant medical products is a top priority in fostering the innovative climate needed to maintain U.S. competitiveness in diagnosing, treating, and preventing disease.

Not all medical product development concerns itself with disruptive technologies such as new molecular entities, significant new biologics, radically innovative medical devices, or combinations of these. While, in

Arizona	Arizona State University
California	Stanford University
	University of California San Francisco
	San Diego State University—Center for Bio/Pharm and Biodevice Development
	University of Southern California
Colorado	Colorado State University
Connecticut	University of Connecticut
Florida	University of South Florida
	University of Florida College of Pharmacy
Georgia	Georgia Technical Institute
	Emory University
	University of Georgia, College of Pharmacy
Illinois	Illinois Institute of Technology
Indiana	Purdue University
Massachusetts	Boston University
	Northeastern University, School of Professional and Continuing Studies
	Regis College
	Massachusetts College of Pharmacy and Health Sciences
Maryland	Johns Hopkins University
	University of Maryland, Baltimore
	Hood College
Michigan	University of Michigan
	Case Western Reserve University
Minnesota	University of St. Thomas
	St. Cloud State University
North Carolina	Campbell University School of Pharmacy
	Duke University
New Jersey	Rutgers, The State University of New Jersey

Figure 1.6 Sampling of schools* with programs related to medical product development.**

*Not a complete list

**Including regulatory affairs, preclinical development, clinical development, science and technology management, translational research, bioengineering

New York	Long Island University—Arnold and Marie Schwartz College of Pharmacy
	St. John's University
Oregon	Oregon Health and Science University
Pennsylvania	Lehigh University
	Drexel University
	Temple University
	University of Pennsylvania
	University of Pittsburgh
Rhode Island	University of Rhode Island
Tennessee	Vanderbilt University
Virginia	University of Virginia
Washington	University of Washington
Wisconsin	University of Wisconsin

Figure 1.6 *Continued.*

concept, translational research is most visibly applied to these truly new healthcare products, its principles are valuable in optimizing development of products that are not so unique. For example, repurposing old drugs for treatment of other target diseases, iterative changes to drug formulation, synthesis versus extraction of active biological agents, and design changes to increase the effectiveness of medical devices in a vastly different demographic setting all have great potential to improve healthcare. All require product development planning, utility assessment, demonstration of preclinical and clinical safety and efficacy, analysis of regulatory and intellectual property impact, market factors analysis, and other activities that benefit from translational approaches applied beyond the very early basic research phase of development. Regardless of the nature or uniqueness of the product, changes in the way those products are developed will be necessary for the United States to effectively compete in this arena. The objective of the following chapters is to help establish intellectual, scientific, logistical, and terminological common ground to foster interdisciplinary collaboration in crossing the bridge from research to medical practice.

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2

Healthcare in the United States

Health is worth more than learning.

—Thomas Jefferson

Medical product development in the United States has been beleaguered by uncontrollably escalating costs, embarrassingly low productivity, clinical failures, legal nightmares ranging from product liability to patent litigation, and oversight by an understaffed and underbudgeted federal regulatory body.

Those involved in medical product development share the same primary goal: to discover, develop, and bring to market new products that enable people to live healthier, more productive, more comfortable lives. Nowhere in the world is this goal more enthusiastically endorsed by the population than in the United States. Yet, from day one in the product development process, medical products manufacturers face challenges that other industries never have to confront.

The United States leads the world in healthcare spending.[1] Health and well-being are so important in this country that in 2012, annual national health expenditures will exceed 17% of the gross domestic product (GDP), or about $9000 per person. This means that in 2012 Americans will have spent over $2.9 trillion on healthcare—about twice the amount spent in 2002. Government projections anticipate that average annual health spending growth will outpace average annual growth in the overall economy. By 2019, national health spending is expected to reach $4.5 trillion and comprise nearly 20% of GDP.[2] Prescription drug expenditures alone have accounted for 10% of the money spent in the United States on healthcare since 2001, and the projections indicate that this percentage will remain relatively stable.

Unlike prescription drug expenditures, spending on medical devices is not specifically tracked by the U.S. Department of Health and Human

Services, but in 2009, the latest year studied, estimated sales of medical devices and in vitro diagnostics totaled $147.0 billion, or 5.9% of total national health expenditures.[3] Biologics represent a substantial segment of the U.S. drug market, and sales were expected to be approximately $60 billion in 2010.[4] Add up the numbers and it becomes clear that the market for prescription drugs and other healthcare products, including medical devices and biological products, is staggeringly huge. Continued growth and profitability, however, depend on a delicate balance of managed care initiatives, federal and international regulatory requirements, generic challenges, liability issues, and the ability of industry suppliers and manufacturers to shorten product development cycles while controlling costs.

Product development in the healthcare field, especially development of medical devices and certain biologics, has all too often been a seat-of-the-pants endeavor, shortchanged in terms of support and understanding by management and by the individuals charged with getting the job done. But with recent developments in healthcare management, and with sweeping changes in global clinical, regulatory, and quality requirements, manufacturers will no longer be able to effectively compete in the arena of healthcare products without making equally sweeping changes in the way they develop new products. FDA has taken on a new role in enabling these changes, which will be discussed in Chapter 3.

Manufacturers of healthcare products today are obligated to do more than simply provide evidence to FDA that their products are safe and efficacious. Growing concerns about the cost and quality of healthcare in the United States will dictate that in order for a new product to be accepted, reimbursed, and perhaps even approved, the use of that product will have to provide favorable outcomes in terms of attributes such as:

- Clinical utility in uncontrolled real-life use situations
- Quality of life for the patient, following the treatment
- Cost-effectiveness
- Addressing unmet medical needs
- Suitability for use in pediatric and aged populations

Thus, a successful product development process will need to factor in therapeutic, humanistic, and economic performance.

It takes a lot of money and time to develop and launch a healthcare product. It is estimated that in the United States, about 10 to 15 years and over $1.3 billion are needed to develop and obtain approval for a new drug.[5] Investment requirements for the development of new therapeutic biologics are similar. Because the medical device arena is much more diverse and

complex, it is difficult to estimate average development times. Average time from concept to commercialization for medical devices can range from two years to 10 years depending on the type of regulatory application required.

Regulatory requirements and quality standards are becoming more demanding, in part because of the desire to market new products outside of the United States. The shrinking of the world through globalization of medical product businesses is a fact of life, for a variety of reasons: (1) the domestic market is becoming increasingly saturated, so that going global is one of the few remaining ways to grow; (2) the pressures of managed care and cost containment in the United States are making it more difficult to increase domestic sales of products that do not have demonstrated outcomes advantages when compared with available lower-priced alternatives; (3) small companies partner with or get acquired by large companies, the overwhelming majority of which have a multinational presence; and (4) large, multinational companies want products that they can market globally. Yet many healthcare companies are poorly prepared to integrate their product development plans with the elements of cultural biases and preferences in medical and surgical practices, differing expectations of acceptable clinical outcomes, and variability in regulatory and quality requirements.

Harmonization of domestic requirements, as defined by FDA, with those set forth by the International Conference on Harmonization (ICH) directives, will be a process requiring ongoing evolution and refinement. One thing is certain: harmonization will directly affect the way product development is planned, executed, and documented.

Because of the enormous investments required for regulated healthcare product development, a shotgun approach often used with nonmedical product categories—in which large numbers of new products are introduced in hopes of ending up with at least one big winner—is not possible. Extraordinary focus and foresight are necessary. Evaluation of a myriad of ideas and opportunities against well-defined criteria will help ensure that resources are directed at a select few of those opportunities—those that will lead to successful and profitable new products.

Even though the pharmaceutical/medical device industry spends proportionately more on R&D as a percentage of sales than other industries, much of that money ends up being misdirected into activities that do not yield information that is useful or new products that are profitable. Industrial R&D intensity and expenditure do not guarantee success. The R&D efforts must be coupled to product and process developments that will sustain the company through the present and into the future. It is not uncommon for 50% or more of what is called R&D activity to be delegated to work that is not research or development related. Requests for technical fixes for

existing products with design flaws usually top the list. Responding to field sales forces when help is needed with customer questions or problems, and revalidating processes and products after the company makes changes in materials, equipment, or manufacturing location are also typical. Add to this the time taken up in general administrative tasks, various updates and presentations, and training programs, and it's clear that not much time may be left for developing new products or technologies.

For a healthcare company to attain or sustain leadership, it will require the timely development and launch of new products that are safe and effective, meet both recognized and unarticulated user needs, and provide necessary and desirable outcomes. Creating and using a system of *product development planning* will substantially increase the probability of achieving these goals. Product development planning should be thought of as the application of total quality management (TQM) principles to new healthcare products.

Product development planning is an integrative approach to addressing both long-term and short-term needs and requirements for new products (see Figure 2.1). Although each component section of product development planning will be discussed separately in this book, in actual practice the components are inseparable. Each component draws on, as well as contributes to, every other component.

Product development planning defines a technology strategy by linking technology forecasting—as a vision of the future—with an ongoing assessment of existing, new, emerging, and embryonic technologies. The technology strategy, in turn, provides the foundation and direction for a portfolio of product development project opportunities. Finally, quality management of this development portfolio depends on successful implementation of a sound product development process. The major components of the product development process, development portfolio management, technology assessment, and technology forecasting overlap in their contributions to short-, medium-, and long-term strategy for the growth and evolution of the company (see Figure 2.2).

Firmly anchored in the present, the product development process deals with the immediacy of identified active projects; its impact on the future is dependent on the development timeline of each project. Portfolio management ensures the proper mix of product development projects and of their sequence and phasing; its impact is linked to the present and near future through monitoring and management of active ongoing projects, and to the mid-term future through staged application of the product development process to other identified projects. Technology assessment spans the near to mid-term future by encompassing evaluation of existing, emerging, embryonic, and new technology opportunities. Finally, the mid- to

long-term future is most influenced by the imaginative, visionary exercise of technology forecasting.

Product development planning, especially through implementation of the principles of the product development process, will allow healthcare companies to break out of the trap of technical service disguising itself as R&D and undermining bona fide product development activities. Product design deficiencies and manufacturing problems will be identified and corrected early, making it much less likely that a costly problem will turn up late in the game. The lack of clarity or comfort in the handling and use

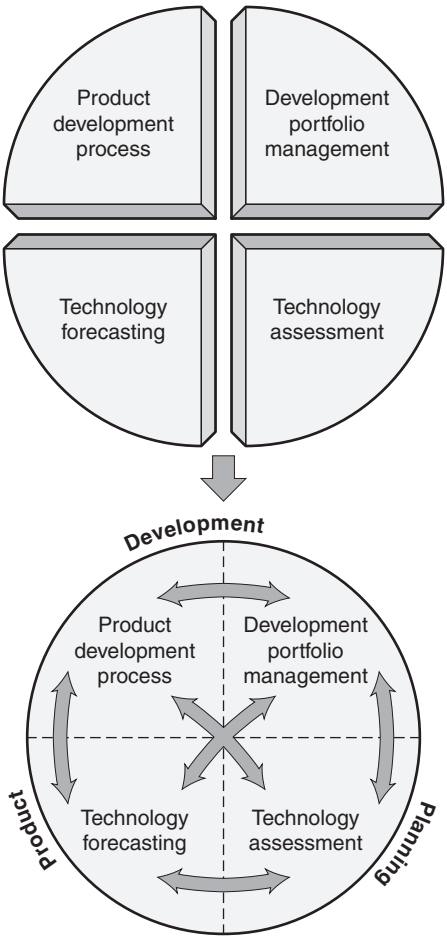

Figure 2.1 Product development planning is an integrative approach.

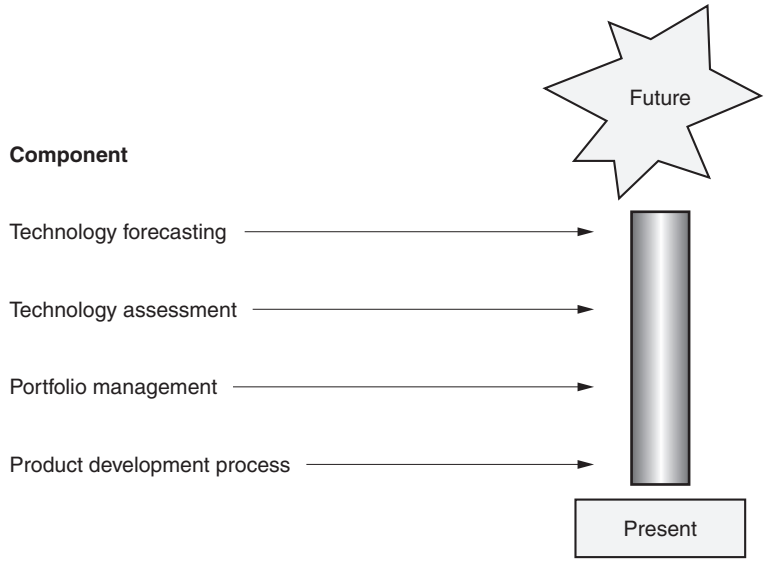

Figure 2.2 Product development planning.

of the product will be minimized or eliminated, reducing the demands for technical assurances, explanations, and support to users of the products. Furthermore, a company will be less likely to suffer the embarrassment and cost of launching a product that is later discovered to have problems with such properties as usability, stability, or packaging. Most importantly, product-associated risks to patients will be reduced.

A few of the techniques and procedural suggestions that follow are especially tailored for the development of one or another category of medical product. For the most part, though, the principles and philosophy are also applicable to all categories of FDA-regulated healthcare products that are the focus of this book: drugs, biologics, and medical devices. A fundamental knowledge and understanding of all three categories of regulated healthcare products is unavoidably important, since new and more sophisticated technological approaches to meeting customer needs have blurred the distinctions between drugs, biologics, and devices. While there may be differences in costs and development times, and in the nature and extent of regulatory and clinical requirements among the various categories of healthcare products, a program of formal and organized product development planning will bring focus and direction to everyone involved in healthcare product development and will add value and profitability to the products being developed.

3

It's Not Your Father's FDA

The "Modernization" of Medical Product Regulation

Laws are like sausages. It is better not to see them being made.

—Otto von Bismarck

Drugs, biologics, and medical devices are among the $1 trillion-plus worth of products regulated by FDA. FDA is charged with protecting American consumers by enforcing the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 (commonly referred to as "the Act"), and a variety of other federal health laws (see Table 3.1).[1] Over the years, critics of FDA became increasingly convinced that the ability of the agency to accomplish its mission was not keeping pace with its obligations. In its effort to maintain the critical balance between the promotion of benefit and the prevention of harm, FDA had become bogged down in a quagmire of complex, unwieldy, and burdensome self-inflicted requirements.

FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997 (FDAMA)

A legislative reform effort to streamline FDA regulatory procedures, to improve the review of regulated products, and to increase and accelerate access to safe and effective medical products culminated with the creation of a modernization initiative. On November 21, 1997, FDAMA was enacted, amending some of the FD&C Act regulations applicable to drugs, biologics, and medical devices.[2] With the passage of FDAMA, Congress enhanced FDA's mission in ways that recognized that the agency needed the capacity to operate in a twenty-first century characterized by increasing technological, trade, and public health complexities.

Table 3.1 Chronology of significant regulations relevant to healthcare product development.

Regulation	Purpose
1902 Biologies Control Act	Ensures purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans
1906 Food and Drugs Act	Prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs
1938 Food, Drug, and Cosmetics Act	Requires new drugs to be shown safe before marketing, and extended control to therapeutic devices and cosmetics
1944 Public Health Service Act	Addresses broad spectrum of health concerns, including regulation of biological products for human use
1962 Kefauver-Harris Drug Amendments	Requires drug manufacturers to prove to FDA the effectiveness of their products and to obtain approval before marketing them
1966 Fair Packaging and Labeling Act	Requires consumer products, including drugs and medical devices, to be honestly and informatively labeled
1968 Radiation Control for Health and Safety Act	Protects public from unnecessary exposure to radiation from radiation-emitting products
1976 Medical Device Amendments	Ensures safety and effectiveness of medical devices, including diagnostic products, and requires manufacturers to register with FDA
1983 Orphan Drug Act	Enables FDA to promote research and approval and marketing of drugs that would otherwise not be profitable but that are needed for treating rare diseases
1984 Drug Price Competition and Patent Term Restoration Act	Allows approval of generic versions of brand-name drugs without repeating safety and efficacy studies, allows brand-name companies to apply for up to five years' additional patent protection to compensate for time lost during FDA approval process
1990 Safe Medical Devices Act	Requires reporting of any medical device causing or contributing to the death, serious illness, or injury of a patient, requires manufacturers to conduct post-market surveillance of implanted devices

Continued

Table 3.1 *Continued.*

Regulation	Purpose
1992 Medical Device Amendments	Expands requirements for registration, certification, documentation, reporting, and surveillance of medical devices
1992 Prescription Drug User Fee Act	Requires drug and biologics manufacturers to pay fees to FDA for product applications and supplements
1997 Food and Drug Administration Modernization Act	Makes numerous changes to the rules governing FDA and regulated industries and enacts many FDA initiatives in the Reinventing Government program
2002 Medical Device Fee and Modernization Act	Allows FDA to collect fees to review medical submissions
2007 Food and Drug Administration Amendments—Act	Reauthorizes previous acts and amendments and makes important provisions for increased safety and modernization

FDAMA comprises major reforms to the way FDA regulates products under its jurisdiction. The following passages explain some of the most important provisions of the act that apply to medical products.

Prescription Drug User Fees

The act reauthorizes the Prescription Drug User Fee Act of 1992 (PDUFA). These user fees have allowed FDA to add resources, reducing the review time for drugs and biologics. Codified initiatives include measures to:

- Modernize the regulation of biological products by bringing them in harmony with the regulations for drugs
- Eliminate the need for establishment license application for biologics
- Eliminate the batch certification and monograph requirements for insulin and antibiotics
- Streamline the approval processes for drug and biological manufacturing changes
- Reduce the requirements for environmental assessment as part of a product application

- Increase patient access to experimental drugs and medical devices
- Accelerate review of important new medical products
- Establish a database on clinical trials, which will be accessible by patients

Information on Off-Label Use and Economics

The law removes the long-standing prohibition on dissemination by manufacturers of information about unapproved uses of drugs and medical devices. The act allows a firm to disseminate peer-reviewed journal articles about an off-label indication of its product, provided the company follows specific guidelines established by FDA. Drug companies are also allowed to provide economic information about their products, under specific FDA guidelines.

Risk-Based Regulation of Medical Devices

FDAMA enhances FDA's recent measures to focus its device review resources on medical devices that present the greatest risks to patients. For example, the law:

- Exempts Class I devices from premarket notification if not intended for a use that is of substantial importance in preventing impairment of human health, or do not present a potential unreasonable risk of illness or injury
- Directs FDA to focus its post-market surveillance on higher-risk devices
- Allows the agency to implement a reporting system that concentrates on a representative sample of user facilities (for example, hospitals and nursing homes) that experience deaths and serious illnesses or injuries linked with the use of medical devices
- Expands an ongoing program under which FDA accredits outside "third party" experts to conduct the initial review of all Class I and low- to intermediate-risk Class II devices
- Specifies that an accredited third-party person may not review devices that are permanently implantable, life-supporting, life-sustaining, or for which clinical data are required

Standards for Medical Products

Although FDAMA reduces or simplifies many regulatory obligations of manufacturers, it does not lower the standards by which medical products are introduced into the marketplace. FDAMA:

- Codifies the agency's current practice of allowing, in certain circumstances, one clinical investigation as the basis for approval of a new drug or biologic; however, it does preserve the presumption that, as a general rule, two or more adequate and well-controlled studies are needed to prove safety and effectiveness
- Specifies that FDA may keep out of the market medical devices whose manufacturing processes are so deficient that they could present a serious health hazard
- Gives the agency authority to take appropriate action if the technology of a device suggests that it is likely to be used for a potentially harmful unlabeled use

The New FDA

Since FDAMA, there have also been a number of additional amendments to the FD&C Act:

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) amends the FD&C Act to grant the Center for Devices and Radiological Health (CDRH) new responsibilities and resources, including collection of user fees for premarket review of medical devices.[3] These fees are analogous to the PDUFA fees discussed earlier.

Best Pharmaceuticals for Children Act of 2002 (BPCA) amends the FD&C Act to encourage more studies in children, and promotes the development of treatments for children to improve the safety and efficacy of pharmaceuticals for children.

Pediatric Research and Equity Act of 2003 (PREA) amends the FD&C Act to require New Drug Applications (NDAs) and Biologics Licensing Applications (BLAs), or supplements to applications, for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to include a pediatric assessment unless the applicant has obtained a waiver or deferral.

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[4] reauthorizes PDUFA, MDUFMA, BPCA, and PREA. Among other things, the FDAA of 2007 also provides for:

- Additional encouragement of specialized pediatric medical device development
- The creation of a foundation to modernize product development, accelerate innovation, and enhance product safety
- Advisory committee provisions
- Clinical trial registries requirements
- Provisions intended to enhance drug safety

In addition to the changes described above resulting from the implementation of the various amendments to the FD&C Act, FDA has taken on a new look in a wide variety of areas with the establishment of new offices and new initiatives, some examples of which are shown in Figure 3.1. Significant areas of activity include the following:

Office of Combination Products. FDA established an Office of Combination Products (OCP) to streamline the regulatory pathway for complex drug-device, drug-biologic, and device-biologic combination products.

Office of Translational Sciences. The Center for Drug Evaluation and Research (CDER) Office of Translational Sciences (OTS) promotes efficient and informative study designs and data analysis methods to quantitatively evaluate the efficacy, safety, and dosing of drugs through collaboration between the Office of Biostatistics (OB), Office of Clinical Pharmacology (OCP), and other offices in CDER and centers in FDA. The OTS fosters novel drug development strategies through research and application of statistical and mathematical modeling and simulation techniques in the review and analysis of data in the areas of exposure response, pharmacokinetics, pharmacodynamics, pharmacogenomics, bioequivalence assessment, clinical trials, quantitative risk assessment, toxicology, and product quality assessment.

Critical Path Initiative (CPI). In 2004, FDA launched a program for a national strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. The initiative is discussed in Chapter 1.

Increased Surveillance of Medical Devices. FDA announced that it will require manufacturers of certain critical medical devices to conduct post-market surveillance on those products. The devices are those for

Critical Path Initiative (CPI) is FDA's national strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured.

Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) Initiative is aimed at modernizing and strengthening the agency's oversight and protection of subjects in clinical trials and the integrity of resulting data.

FDA Transparency Initiative includes addressing ways FDA can become more transparent to regulated industry to foster a more efficient and cost-effective regulatory process.

CDRH's Medical Device Innovation Initiative includes a novel priority review pathway for bringing pioneering medical devices to market swiftly and safely; it promotes the exchange of ideas between external and internal innovators, device experts, and FDA staff—building a framework for recognizing promising ideas early and incentivizing innovation for years to come.

FDA Regulatory Science and Facilities Initiative will strengthen the core regulatory scientific capacity that supports all elements of the FDA mission; this initiative will help modernize and streamline the regulatory pathways that industry relies on to bring new, innovative products to market.

Figure 3.1 Examples of recent FDA initiatives affecting product development. *Source:* FDA.

which failure would reasonably be expected to cause severe adverse consequences. This surveillance will provide a way for FDA (and manufacturers) to identify problems that were not identified during the course of product development.

Approval of Some Products Based on Animal Data. FDA has amended drug and biologics regulations to allow approval of certain drugs and biologics, specifically some products intended to reduce or prevent serious or life-threatening conditions, without requiring human clinical trials for efficacy. If studies on humans are not ethical or feasible, the agency may accept animal efficacy data in lieu of human clinical trials data. The new rule reflects the unfortunate state of the human condition in that FDA regards it as especially applicable to therapies used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear weapons agents.

Risk-Based Approach to Pharmaceuticals Manufacturing. FDA announced that it is undertaking an initiative called "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" to integrate science-based risk management with integrated quality control systems. The purpose of the endeavor is to direct resources to ensure that drug and biologics manufacturing will better serve the cause of patient safety. The agency

will match its level of effort against the magnitude of possible risk associated with a product and its manufacturing. This will increase the level of responsibility for manufacturers of high-risk products, while alleviating some burden on manufacturers of low-risk products.

Withdrawal of Outdated Draft Proposals. FDA is withdrawing many old proposed actions and rules that were never finalized and that are no longer regarded as agency priorities. There were so many proposed rules and other actions that had never been finalized or had never been implemented that the administrative requirements and review backlog became unmanageable by FDA. The move is expected to clarify the status of old projects, simplify and streamline FDA's rulemaking process, and to focus agency resources on more relevant proposals. Withdrawing a proposal doesn't preclude FDA from reissuing the same or a similar proposal in the future.

Strategic Plan for Advancement of Regulatory Science. In August 2011, FDA published a strategic plan *designed to allow the agency to both meet today's public health needs and to be fully prepared for the challenges and opportunities of tomorrow. The science priority areas identified in the plan are intended to:*

- Modernize toxicology to enhance product safety
- Stimulate innovation in clinical evaluations and personalized medicine
- Improve product development and patient outcomes
- Support new approaches to improve product manufacturing and quality
- Ensure FDA readiness to evaluate innovative emerging technologies
- Harness diverse data through information sciences to improve health outcomes
- Implement a new prevention-focused food safety system to protect public health
- Facilitate development of medical countermeasures to protect against threats to U.S. and global health and security
- Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products

One important point for those unaccustomed to or uninitiated in regulatory matters is that despite FDA's efforts to streamline regulatory processes,

a company does not obtain FDA clearance or approval to market a new healthcare product by simply filling out an application form. Submitting the documentation for a 510(k), PMA, NDA, or BLA is not like applying for a credit card or a driver's license. Depending on the product, these submissions may range in length from less than 100 pages (for example, for some medical devices) to hundreds of thousands of pages (for example, for some drugs with extensive clinical data).

While there is not a straightforward application form specifically appropriate for each general class of products (devices, drugs, or biologics), there is a general format concerning the minimum information and data that FDA expects to see in each type of submission for approval or clearance. FDA has generated voluminous quantities of guidance and regulations publications pertaining to specific categories of regulated healthcare products. There is a distinct difference between guidance and regulations. *Regulations* are federal law. *Guidances* describe FDA's current thinking on a topic and should be viewed only as nonbinding recommendations, unless specific regulatory or statutory requirements are cited. According to FDA, the use of the word *should* in published guidances means that something is suggested or recommended, but not required. However, unless there is a compelling reason not to follow a guidance, one should regard guidance points as being very strongly recommended.

Regulations applicable to drugs, biologics, and medical devices will continue to change and evolve in response to technical developments, market urgency, and political pressures. Direct consultation with FDA, attention to the guidance documents, and strict adherence to issued regulations will contribute to the definition of the structure and substance of a particular submission.

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4

Classifying Medical Products

Lions, and tigers, and bears! Oh, my!

—Dorothy in *The Wizard of Oz* (1939)

Before going on to more detailed consideration of how to create and implement product development planning that will bring a new product to market, it is important to understand how medical products are regulated in the United States under the provisions of FDAMA, and in general terms, the differences and similarities in what is required for these products to be legally sold.

Whether a product is classified as a drug, biologic, or medical device is not always intuitively obvious. In fact, some products now defined as medical devices were previously classified as drugs. Biologics are also legally defined either as drugs or devices and are therefore also subject to the provisions relating to drugs or devices.[1] Biologics also are common components of medical devices, especially in vitro diagnostic devices, and in the marketplace, there is generally no perceived distinction between drugs and therapeutic biologics such as vaccines or blood clotting factors.

Despite some significant overlap in the attributes of each category of product, a different suborganization, or center, within FDA has been charged with the primary responsibility of regulating each category. However, even FDA has had to cry "uncle" and admit that in a substantial number of cases, there is a need for review by more than one center, even though only one center would have primary regulatory jurisdiction.

Theoretically, FDA's determination of whether to classify a product as a drug, a biologic, or a medical device is based on the statutory definitions of these terms as applied to the scientific data concerning the specific product that are available to FDA at the time the classification determination is made. This is easier said than done, and frequently there are challenging

Table 4.1 Not all products of biological source are regulated by CBER.

Product (Human)	FDA Jurisdictional Center		
	CBER (Biologics)	CDER (Drugs)	CDRH (Devices)
Corneas	✓		
Corneal lenticules			✓
Cartilage	✓		
Collagen			✓
Arteries and veins for vascular grafts (except for preserved umbilical cord veins)	✓		
Preserved umbilical cord veins			✓
Femoral veins for A-V shunts			✓
Oocytes	✓		
Estrogen		✓	
Blood clotting factors	✓		
Enzymes to dissolve blood clots		✓	
Pancreatic islet cells for transplantation	✓		
Insulin		✓	
Pancreas for transplantation	*	*	*

*Vascularized human organ transplants such as kidney, liver, heart, lung, or pancreas are not regulated by FDA.

Source: FDA.

interpretive issues that arise when determining which category a given product best fits. As shown by the examples in Table 4.1, there can be non-obvious different classifications of products from the same or similar biological source. In an attempt to keep things as straightforward as possible, each major medical product category is defined and discussed below.

DRUGS AND BIOLOGICS

Distinguishing between drugs and biologics is extremely complicated. Do not attempt to do this at home.

Drugs

FDA regulates prescription and over-the-counter medicines for humans through its Center for Drug Evaluation and Research (CDER). The primary responsibility of CDER is to approve the marketing of drugs that are effective for their labeled indications, provide benefits that outweigh their risks, are of high quality, and have directions for use that are complete and honestly communicated. The regulatory authority for drugs is contained in the FD&C Act, which defines drugs principally as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals . . . intended to affect the structure or any function of the body of man . . . ." (see Figure 4.1).[2]

Before a new drug under development can be tested on humans, an Investigational New Drug (IND) application must be filed. The minimum information included in an IND is shown in Figure 4.2a. In reviewing an IND, FDA is most concerned with determining that adequate data have been provided to establish that the new product is reasonably safe to use on human subjects in clinical trials, and that the proposed clinical trial will generate useful and acceptable data. If the IND is approved, the first step has been taken in allowing the as yet unapproved drug to be evaluated in clinical trials (that is, trials on humans) without breaking the law. As shown in Figure 4.2b, clinical trials of drugs generally involve successful completion of three or more phases of testing. Clinical trials are performed with the consent of participating hospitals and institutions, and, upon the conclusion of a successful clinical trial, a New Drug Application (NDA) is submitted to FDA for review. If the NDA is approved, a drug may be legally marketed.

The term "drug" means:

(A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

Figure 4.1 Definition of a drug.
Source: Federal Food, Drug, and Cosmetic Act.

- Information about the sponsor and the investigators
- The name of the drug, the mechanism of action, the marketing history, and a brief description of the clinical trial
- A summary of all safety and previous clinical data
- A plan for clinical investigation
- A description of the drug composition, the method of manufacture of the drug, and quality control measures used in production
- A description of pharmacology and toxicology studies and results upon which the sponsor has determined it is reasonably safe to conduct clinical trials
- A summary of all other previous use of the drug in humans
- Additional information, such as dependence/abuse potential or radioactive drug information

Figure 4.2a Minimum information included in an IND.

- Phase I
  - Pharmacology/pharmaocokinetics
  - Basic safety and early evidence of activity
- Phase II
  - Efficacy/proof of concept
- Phase III
  - Adequate and well-controlled trials to support marketing approval
- Phase IV
  - Post-marketing commitments

Figure 4.2b Clinical trial testing phases.
Source: FDA CDER.

Biologics

Biologics are medical preparations made from living organisms and their products (with exceptions, as discussed below), and the category includes vaccines, blood products, certain diagnostic products, and biotechnology-derived products. The FDA's Center for Biologics Evaluation and Research (CBER) is responsible for ensuring the safety, efficacy, potency, and purity

The term "biological product" (biologic) means:

A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Figure 4.3 Definition of a biological product.
Source: Public Health Service Act, as amended.

of biological products used to treat, prevent, or cure diseases. The center regards its mission as protection and enhancement of the public health through regulation of biological and related products according to statutory authorities, which for biologics resides both in the Public Health Service (PHS) Act[3] and the FD&C Act. The definition of a biologic, which was modified recently, states that:

> The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Figure 4.3).[4]

As is the case for drugs, an IND and clinical trials are generally required for biological product approval.

There have been numerous and profound changes in the regulation of biologics, and many products previously regulated by CBER have been reclassified as drugs and are now under the jurisdiction of CDER (under either the FD&C Act or the PHS Act, as appropriate). Note, however, that hormones such as insulin, glucagon, and human growth hormone are regulated as drugs under the FD&C Act, not as biological products under the PHS Act!

CBER, for the time being, will concentrate its expertise and effort in the areas of vaccines, blood safety, gene therapy, and tissue transplantation. Biologics product classes that remain at CBER are:

- Gene therapy products, specifically human gene therapy/gene transfer, which is the administration of nucleic acids, viruses, or genetically engineered microorganisms that mediate their effect by

transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient, or altered in vivo by gene therapy products administered directly to the recipient.

- Vaccines and vaccine-associated products, regardless of their composition or method of manufacture, intended to induce or enhance a specific immune response to prevent or treat a disease or condition or to enhance the activity of other therapeutic interventions.
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.
- Antitoxins, antivenoms, and venoms.
- Blood, blood components, plasma-derived products (for example, albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors) including recombinant and transgenic versions of plasma derivatives such as clotting factors, blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations including radiolabeled or conjugated forms, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents.
- Human cells, tissues, and cellular and tissue-based products (HCT/Ps), which includes HCT/Ps containing cells that have been harvested following in vivo administration of a CDER-regulated growth factor, cytokine, or monoclonal antibody, as well as HCT/Ps requiring ex vivo manipulation.
- Xenotransplantation products—including live cells, tissues, or organs from a nonhuman animal source—and human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

Some products that meet the definition of drugs or medical devices, that also meet the definition of biological products, might be classified as drugs or devices. On the other hand, they might be classified as biological products, rather than as devices or drugs, and be subject to licensure under the PHS Act. Naturally, this is not easily worked out, but FDA will review information on a product and determine classification upon request by a sponsor.

FDA Consolidation of Drugs and Biologics

Biologics are made from a variety of natural resources—human, animal, and microorganism—and may be produced by biotechnology methods. They may be composed of, for example, sugars, proteins, or nucleic acids, or a combination of these substances. They may also be living entities, such as cells and tissues. But, as mentioned above, not all biological products are regulated as "biologics." Yes, that is aggravatingly confusing.

In the marketplace, a distinction between drugs and many biologics is typically not made, and figures related to use or sales of both are often lumped together in the category of pharmaceuticals. Likewise, in terms of product development, the principles and challenges encountered in the two areas are often fundamentally the same. But FDA was resistant to act on the similarities, and until the implementation of FDAMA, FDA regulated all biologics in a different manner than drugs. Although the agency had recognized the similarities between the definitions of drugs and of biologics, the FDA's position had been that there were important differences between the two that required different regulatory processes. According to FDA, a drug is typically a chemical entity that can be well characterized with respect to its physical attributes, including its structure, whereas a biologic is typically a complex mixture of components that can not be separated and characterized.

Before the implementation of FDAMA, the perceived inability to fully characterize final biological products led FDA to require that the regulation of biologics rely heavily on in-process testing and validation of production. Thus, a significant difference between FDA approval processes for new drugs and biologics existed. Marketing a new drug in the United States required *approval* of a New Drug Application (NDA) for the drug *product*. In comparison, marketing of a biologics product required separate processes to obtain (1) a *license* for the *biologic product* through approval of a product license application, or PLA, and (2) a *license* for the *manufacturing facility* for the biologic through approval of an establishment license application, or ELA. As a result of government reinvention and modernization efforts to minimize the review and approval of new biologics, the separate ELA has now been eliminated, and the PLA has been replaced by a single Biologics License Application (BLA). This move reflects a harmonization of biologics regulation with that of the NDA process for drugs.

In 2003, FDA completed a consolidation of certain biologic product reviews from CBER to CDER with the objective of producing a more efficient, effective, and consistent review program for drugs and biologics.

CDER created two new offices to accommodate the former CBER staff:

- The Office of Drug Evaluation VI, within the CDER's Office of New Drugs.
- The Office of Biotechnology Products (OBP), within the CDER's Office of Pharmaceutical Science. The OBP is responsible for therapeutic protein and monoclonal antibody products.

The product categories previously regulated by the CBER as biologics that have now been transferred to CDER include:

- Monoclonal antibodies for in vivo use.
- Most proteins intended for therapeutic use, including cytokines (for example, interferons), enzymes (for example, thrombolytics), and other novel proteins (except for those such as vaccines and blood products, which are specifically assigned to CBER). The category now regulated by CDER includes therapeutic proteins derived from plants, animals, humans, or microorganisms, and recombinant versions of these products. Exceptions to this rule are blood coagulation factors—both recombinant and human plasma–derived—which remain under the jurisdiction of CBER.
- Immunomodulators, which are proteins or peptides such as cytokines, growth factors, chemokines, and so on, that are not antigen-specific and that are intended to treat disease by inhibiting or modifying a preexisting immune response, and proteins or peptides intended to act in antigen-specific fashion to treat or prevent autoimmune diseases by inhibiting or modifying preexisting immune responses.
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease, or otherwise alter the production of cells in vivo. This category includes growth factors, cytokines, and monoclonal antibodies, as well as nonbiological agents, administered as mobilizing agents for their direct therapeutic effect on the recipient, as well as growth factors, cytokines, and monoclonal antibodies administered for the purpose of subsequently harvesting the mobilized, stimulated, decreased, or otherwise altered cells for use in a human cellular or tissue-based product.

Regardless of which FDA center has review jurisdiction, the safety, purity, potency, and efficacy of drugs and biologics must be established to the satisfaction of FDA before a product will be approved for marketing.

MEDICAL DEVICES

Responsibility for ensuring the safety and effectiveness of medical devices and radiation-emitting products falls to the FDA Center for Devices and Radiological Health (CDRH). There are thousands of types of medical devices, from heart pacemakers to wheelchairs, from in vitro diagnostics to the software that controls automated devices. Ultrasound and X-ray machines, surgical lasers, and video display terminals used with medical equipment are examples of radiation-emitting medical devices.

Even though all of these medical devices fall under the jurisdiction of CDRH, the vagaries of FDA guidelines and regulations can make dealing with this category of healthcare products a nightmare. A bit of history might help explain some of the confusion and complexity.

Although the FD&C Act of 1938 gave FDA the authority to regulate medical devices in order to ensure their safety, FDA found itself in a position, familiar to everyone in middle management, of having a great deal of responsibility but insufficient authority to meet the demands of the responsibility. At that time, a medical device, defined by the legislation as "any instrument, apparatus, or contrivance, including any of its components or parts, intended for use in the diagnosis, cure, treatment, or prevention of disease in man or other animals," could be marketed virtually at whim, whether or not it worked or was safe to use. If a device was determined to be in violation of the Act—if it was considered adulterated or included any filthy, putrid, or decomposed substance, or if it was prepared, packed, or held under unsanitary conditions—FDA could seize the product. It could also request an injunction against its production, distribution, or use, and could even recommend criminal prosecution of the manufacturer or other responsible parties. What FDA could not do, however, was require any kind of testing or approval of medical devices *before* they could be marketed. Yet, a 1962 amendment to the Act *did* expand testing requirements for new drugs and gave FDA the authority to require premarket approval for drugs.

As years went by and technological advances took medical devices into the realm of highly sophisticated, often invasive products that could have life-or-death impact on the health and safety of a patient, it became clear that FDA didn't have the teeth it needed to accomplish its mission. Problems with some of these critical devices were recognized as having led to numerous patient injuries, and some of the injuries led to deaths.

In 1970 a government panel (chaired by Theodore Cooper, then-assistant secretary of the U.S. Department of Health, Education, and Welfare), was given the responsibility of reviewing the regulation of medical devices. The Cooper committee findings indicated that 10,000 injuries related to medical devices occurred over a 10-year period, and that 751 of the injuries resulted in death. Specific examples disclosed by the Cooper committee during that 10-year period included:

- 300 injuries and 512 deaths attributed to heart valves
- 186 injuries and 89 deaths attributed to pacemakers
- 8000 injuries and 10 deaths attributed to intrauterine devices[5]

Confronted with these dual issues of safety and efficacy, the courts ruled that certain medical devices were, in fact, drugs and could therefore be regulated as such. In other words, FDA could require testing and approval of these critical devices-turned-drugs before they were marketed.

In 1976, the Medical Device Amendments to the Act were signed into law, providing FDA with authority to regulate devices during most phases of their development, testing, production, distribution, and use. The Safe Medical Devices Act (SMDA) of 1990 increased the authority of FDA with regard to medical devices and added such things as design validation, recall authority, tracking requirements, and civil penalties to the laundry list over which FDA had power.

As shown in Figure 4.4, a medical device is now, and until further notice, defined as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory . . . , which is intended for use in the diagnosis . . . , cure, mitigation, treatment, or prevention of disease . . . , and which does not achieve its primary intended purposes through chemical action within or on the body . . . , and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."[6]

The final portion of the definition is what delineates the distinction between devices and drugs. In reality, it is not always easy to determine whether or not a chemical action takes place that influences the action of a medical device, or whether metabolic products of, for example, absorbable devices contribute to efficacy. Furthermore, there is a distinct incentive for device manufacturers not to look for the answer since any finding that the efficacy of a device is based on physiology or biochemistry could lead

The term "device" means: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is

(A) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

(B) 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

(C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Figure 4.4 Definition of a medical device.
Source: Federal Food, Drug, and Cosmetic Act.

to reclassification of the device as a drug or biologic. And that is something device manufacturers do not want. Responding to constant questions and challenges from industry, in 2011 FDA published a draft guidance on interpretation of the term *chemical action* in the definition of medical devices.[7]

More than 1700 major types of medical devices are regulated by CDRH. Many of these devices may be marketed in the United States without FDA review. FDA grants some medical devices clearance to be commercially distributed or marketed through a process known as *premarket notification*, frequently referred to as a 510(k). Other devices must be taken through a more stringent process known as *premarket approval* (PMA). If clinical testing of a new device is required, an Investigational Device Exemption (IDE), which is analogous to the IND required for drugs and biologics, must generally be filed with FDA. Like an IND, an approved IDE provides a manufacturer the opportunity to legally establish the safety and effectiveness in humans of a new product, which has not yet been approved or cleared for marketing, through clinical studies on human subjects. The type of information included in an IDE is given in Figure 4.5. The similarities between an IND and an IDE are readily apparent.

As you might expect, regulating the large and diverse group of products known as *medical devices* is difficult. Accordingly, the review and clearance or approval processes for medical devices range from complicated to baffling.

- Information about the sponsor
- A complete report of prior investigations of the device, including clinical, animal, and laboratory testing; a bibliography of all publications; and a summary of all unpublished information
- An investigational plan
- A description of methods, facilities, and controls used for the manufacture and (if appropriate) installation of the device
- Information about investigators and institutions where investigations will be conducted
- Any other relevant information requested by FDA

Figure 4.5 Minimum information included in an IDE.

COMBINATION PRODUCTS

The term "combination product" includes:

- A product comprising two or more regulated components, that is, 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
- Two or more separate products packaged together in a single package or as a unit and comprising drug and device products, device and biological products, or biological and drug products
- 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, for example, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose
- 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 (Figure 4.6)

As defined in 21 CFR§ 3.2(e), the term combination product includes:

(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;

(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;

(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; or

(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.

Figure 4.6 Definition of a combination product.
Source: CDRH, Office of Combination Products.

As medical product technologies became more sophisticated, with products consisting of elements belonging to different classification groups, FDA faced a major and confounding issue in establishing which review center—CDER, CBER, or CDRH—had jurisdiction for the regulation of such products, and there were more than a few inter-center turf battles. The Office of Combination Products (OCP) was established and given responsibility for the complete regulatory cycle of combination products, including jurisdiction decisions. The OCP will assign a combination product to an FDA center for primary jurisdiction, oversee the timeliness and coordination of reviews involving more than one center, resolve disputes regarding review issues, and review and modify, revise, or even eliminate agreements, guidance documents, or practices, as the office deems appropriate for a specific combination product. Examples of combination products include:

- Drug-eluting cardiovascular stents
- Lumber-tapered fusion devices with genetically engineered human protein

- Dental prophylaxis pastes with drug components
- Human dermal collagen implants for aesthetic use

Data on recent submissions and approval or clearance activities of CDER, CBER, and CDRH are summarized in Tables 4.2 and 4.3. Specific examples of new NME drugs, biologics, and medical devices that have recently received approval or clearance for marketing are given in Tables 4.4, 4.5, and 4.6.

Table 4.2 Number of original drug and biologics applications filed with CDER and CBER.

Application type	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010
NDA*	112	108	122	126	98
BLA**	12	15	18	20	7
NME***	24	29	29	30	22

*New Drug Applications
**Biologics License Applications
***New molecular entities (includes NDA and BLA submissions)

Source: FDA FY 2010 PDUFA Performance Report.

Table 4.3 Major medical device submissions received by CDRH.

Type of submission	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009
Original PMAs	43	25	31	26	20
PMA supplements	712	1113	1087	1448	1394
Original IDEs	226	251	211	216	222
IDE supplements	4264	4485	4345	4409	4281
510(k)s	3130	3240	3192	3363	3597

Table 4.4 Examples of NMEs approved in 2011.

Product (active ingredient)	**Manufacturer**	**Use**
Jakafi (ruxolitinib)	Incyte Corp.	To treat patients with the bone marrow disease myelofibrosis
Xalkori (crizotinib)	Pfizer	To treat certain patients with late-stage (locally advanced or metastatic), non–small cell lung cancers (NSCLC) who express the abnormal anaplastic lymphoma kinase (ALK) gene
Firazyr (icatibant)	Shire Human Genetic Therapies Inc.	For the treatment of acute attacks of a rare condition called hereditary angioedema (HAE) in people ages 18 years and older
Adcetris (brentuximab vedotin)	Seattle Genetics	For the treatment of Hodgkin's lymphoma and ALCL (systemic anaplastic large cell lymphoma)
Zelboraf (vemurafenib)	Genentech	To treat patients with late-stage (metastatic) or unresectable (can not be removed by surgery) melanoma, the most dangerous type of skin cancer
Brilinta (ticagrelor)	AstraZeneca	To reduce cardiovascular death and heart attack in patients with acute coronary syndromes (ACS)
Nulojix (belatacept)	Bristol-Myers Squibb Company	To prevent acute rejection in adult patients who have had a kidney transplant
Incivek (telaprevir)	Vertex Pharmaceuticals	To treat certain adults with chronic hepatitis C infection
Edurant (rilpivirine)	Tibotec Therapeutics	For the treatment of HIV-1 infection in adults who have never taken HIV therapy

Source: FDA, "Spotlight on Drug Innovation" (2011).

Table 4.5 Some recent biologics approvals.

Product	Use	Manufacturer
Anascorp—Centruroides (scorpion) immune F(ab')2 (equine) injection	Treatment of clinical signs of scorpion envenomation.	Rare Disease Therapeutics, Inc.
Spherusol—Coccidioides immitis Spherule-Derived Skin Test Antigen	For the detection of delayed type hypersensitivity to C. immitis in individuals 18–64 years of age, with a history of pulmonary coccidioidomy-cosis.	Allermed Laboratories, Inc.
Adenovirus vaccine live oral type 4 and type 7	Active immunization for the prevention of febrile acute respiratory disease caused by Adenovirus type 4 and type 7. Adenovirus type 4 and type 7 vaccine, live, oral, is approved for use in military populations 17 through 50 years of age.	Teva Women's Health, Inc.
Corifact—factor XIII concentrate (human)	Routine prophylactic treatment of congenital factor XIII deficiency.	CSL Behring GmbH
Glassia—alpha1-proteinase inhibitor (human)	Treatment of chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of alpha-1-proteinase inhibitor (alpha1-PI), also known as alpha1-antitrypsin.	Kamada Ltd.
Provenge—Sipuleucel-T	Treatment of men with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	Dendreon Corp
Actemra—Tocilizumab	For reducing signs and symptoms of moderate to severely active rheumatoid arthritis in adult patients.	Genentech, Inc.
Hizentra—immune globulin subcutaneous (human), 20% liquid	Treatment of primary immunodeficiency (PI).	CSL Behring AG

Source: CBER.

Table 4.6 Recent medical device approvals and clearances.

Device trade name	Submission type	Manufacturer
RX Herculink Elite Renal Stent System	PMA	Abbott Vascular
Pinnacle CoMplete Acetabular Hip System	PMA	DePuy Orthopaedics
MEL 80 Excimer Laser System	PMA	Carl Zeiss Meditec Inc.
ION Paclitaxel-Eluting Coronary Stent System	PMA	Boston Scientific Corporation
AcrySof Toric Intraocular Lens	PMA	Alcon Labs, Inc.
Elecsys Anti-HBc Immunoassay	PMA	Roche Diagnostics Corporation
Exoseal Vascular Closure Device	PMA	Cordis Corporation
Vision One Laser System	510(k)	Lumenis, Inc.
Hybrid PICA Whole-Body MRI System	510(k)	Time Medical Limited
Total Shoulder System	510(k)	Shoulder Innovations, LLC

Source: CDRH.

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5

Product Liability and Product Development

The operation was a success, but the patient died.

—Unknown

Pharmaceutical and medical device industries are major targets of product liability litigation. The very nature of these products makes them vulnerable to litigation, in no small part because:

- Many devices and drugs are used in the treatment of patients who are already ill or injured
- These products may be used in procedures that are invasive or otherwise inherently risky
- Drugs and devices are often used in life-or-death situations in which a product-related risk is recognized but deemed by medical professionals to be outweighed by benefit
- By their very definition, drugs and medical devices are intended to affect the structure or function of the body

Unintended and/or unexpected consequences of the use, overuse, or misuse of drugs and medical devices include other illness, injury, abnormal behavior, brain damage, and deaths. Sometimes, an adverse event occurs often enough and is consistent enough to be clearly associated with a product; frequently, there appears to be a correlation, but compelling evidence that the product caused harm is lacking. In either case, a patient is harmed, and by coincidence or not, the product was used on the patient prior to the occurrence of the harm.

The penalties associated with product liability findings are a nightmare for medical product manufacturers. Manufacturers and sellers have been required to pay staggering amounts of money to patients for damages

Table 5.1 Examples of U.S. national class action product liability settlements.

Product	Purpose	Settlement (approximate)*
Vioxx	Anti-inflammatory drug	$4.85 billion
Redux, Pondimin (Fen-Phen)	Weight control drug	$3.75 billion
Inter-Op	Hip and knee replacements	$1 billion
Avandia	Type 2 diabetes drug	$460 million

*May not include legal costs or non–class action settlements.

or injuries suffered because of product defects. A few examples of some recent headline-grabbers are shown in Table 5.1. Product liability lawsuits can also have a significant negative effect on the resources, reputation, and value of a company.

PREEMPTION

Preemption is based on the Supremacy Clause of the U.S. Constitution, which states that the laws of the United States shall be the supreme law of the land. Simply put, preemption mandates that a state law that conflicts with federal law is "without effect." Preemption supersedes rights of the plaintiff to recover compensation for their injuries—restricting the authority of state courts—and has been raised as a defense in all drug and device cases for years. Thus, preemption is generally regarded favorably by manufacturers, and unfavorably by anyone who has been injured by a product. There are certain exceptions that apply to preemption, such as fraud.

There is a misconception that FDA clearance or approval of a product for marketing automatically confers legal immunity to product liability. That is not necessarily the case. In fact, while product liability actions do sometimes arise during preapproval clinical trials for a product, most product liability exposure occurs after the product is on the market—which means after regulatory requirements have been met and the product has been cleared or approved by FDA.

MEDICAL DEVICES

For many years, medical device manufacturers were essentially protected from liability for devices that had received marketing clearance or

approval from FDA because of an interpretation of certain provisions of the Medical Device Amendments of 1976. The free ride ended for some devices with a watershed decision by the U.S. Supreme Court in 1996, which established that consumers injured by certain faulty medical devices can seek damages against the manufacturer under state law, even if the devices comply with FDA regulations.[1] In other words, the federal law does not preempt state law with regard to certain medical device product liability. While the Supreme Court ruling on the case in point applies to devices cleared for marketing under the provisions of 510(k) Premarket Notification, the principles had on occasion been successfully applied to devices approved by FDA through the premarket approval (PMA) process.[2]

However, that option changed in 2008, when the U.S. Supreme Court held that state claims regarding PMA devices are, in fact, preempted by federal law.[3] The case has significant implications for the medical device industry because, while affirming preemption of PMA-approved devices, the court did not overrule the 1996 decision that preemption does *not* apply to 510(k) devices. The decision is mainly based on the requirement for data demonstrating the safety of the product before a PMA product receives federal approval for marketing. In contrast, a 510(k) is a notification of intent to market a device based on a manufacturer's claim that it is substantially equivalent to a medical device marketed before 1976, when no such data were required for medical devices.

DRUGS

In 2009, the U.S. Supreme Court held that claims against a drug manufacturer were not automatically preempted by federal law or FDA regulations. The decision was based on the court's opinion that FDA approval of a drug may be insufficient to provide a conflict preemption defense, and that congress intended FDA regulations to be supplemented by state tort suits rather than be preemptive of such suits.[4]

Slightly more than two years later, in 2011, the same court, somewhat counterintuitively, held that generic drugs *are* preempted.[5] No, that is not a typo.

So, in a nutshell:

- Medical devices that have gone through FDA's PMA process *are* preempted
- Medical devices marketed via 510(k) clearance, a much less burdensome standard, *are not* preempted

- Brand name drugs *are not* (necessarily) preempted
- Generic versions of brand name drugs *are* preempted

There are important questions that remain. With FDA's concerted effort to down-classify medical devices, what will happen to the preemption status of a Class III PMA device that is reclassified as Class II 510(k) during the course of a product liability lawsuit? Can the manufacturer of a brand-name drug potentially be held liable for an injury allegedly caused by the generic version of the drug?

Basis of Product Liability

Product liability may be established by evidence that the product causing the harm was not reasonably fit, suitable, or safe for its intended purpose because of design defects, warning defects, or manufacturing defects (see Figure 5.1)[6]

Design Defects

A product design may be inherently dangerous, or may be designed in a manner that is prone to failure in a way that can cause harm. Some products

A product:

(a) contains a *manufacturing defect* when the product departs from its intended design even though all possible care was exercised in the preparation and marketing of the product;

(b) is *defective in design* when the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design by the seller or other distributor, or a predecessor in the commercial chain of distribution, and the omission of the alternative design renders the product not reasonably safe;

(c) is defective because of *inadequate instructions or warnings* when the foreseeable risks of harm posed by the product could have been reduced or avoided by the provision of reasonable instructions or warnings by the seller or other distributor, or a predecessor in the commercial chain of distribution, and the omission of the instructions or warnings renders the product not reasonably safe.

Figure 5.1 Establishing product defects for product liability.
Source: Restatement (Third) of Torts: Prod. Liab. §2 (1998).

may exacerbate preexisting injuries or illnesses of patients. Properly executed product development activities, such as application of design controls and attention to human factors, are crucial in minimizing the occurrence of design defects.

Warning Defects

Any known or reasonably anticipated hazard associated with the use of a medical product should be made clear and obvious in its labeling and instructions for use. Although many medical professionals and/or patients make no attempt to read package inserts and other labeling, a manufacturer has a duty to minimize known or foreseeable risks through effective warnings that clearly convey:

- The nature of the hazard
- The level of the hazard
- Consequences of the hazard
- The means to avoid the hazard

Product development teams must be able to accurately and effectively communicate the required information to those within their company who are responsible for labeling development.

Manufacturing Defects

Even the most well-designed, well-labeled product is a lawsuit incubator if it has not been manufactured according to the manufacturer's specifications. This includes design specifications and manufacturing process specifications. Deviation from specifications during manufacturing may produce a product that might malfunction or otherwise be dangerous. Those involved in product development typically have limited influence on post-launch manufacturing of a marketed product.

The Role of Product Development Planning

With the likely exception of manufacturing defects, product development holds the central obligation in the prevention of product liability. To avoid product liability, the risk of a product causing harm must be minimized. To this end, as shown in Figure 5.2, responsibilities and goals for product development teams include the following:

- *Design for foreseeable risks.* Gain adequate familiarity with the environment in which the product is intended to be used, and have the imagination to anticipate when, where, how, why, and by whom the products are reasonably likely to be misused.
- *Test the product.* Sufficient early prototype or product testing can reveal defects and deficiencies.
- *Assess the risk of injury.* Conduct risk analysis with a multifunctional team to cover as many aspects of product use and foreseeable misuse as possible.
- *Communicate findings.* Clearly inform decision makers about risks and means to avoid or minimize the risks.

Figure 5.2 Responsibilities of product development planning in minimizing future product liability problems.

1. *Design for foreseeable risks.* This means having adequate familiarity with the environment in which the product is intended to be used, and having the imagination to anticipate when, where, how, why, and by whom the products are reasonably likely to be misused.
2. *Test the product.* Sufficient early prototype or product testing can reveal defects and deficiencies.
3. *Assess the risk of injury.* Conduct risk analysis with a multifunctional team to cover as many aspects of product use and foreseeable misuse as possible.

Processes for achieving these objectives are discussed elsewhere in this book. If these steps result in the identification of safety risks that may be associated with the normal use of the product or with foreseeable misuse of the product, important decisions will fall on the shoulders of the product development team. Questions that will need to be addressed and resolved are:

1. Have all of the safety risks been identified for normal use of the product?
2. Have all of the safety risks been identified for foreseeable misuse of the product?
3. To what extent are the identified risks minimized through routine design development procedures, product testing, and application of industry standards?

4. To what extent will warnings and anticipated adherence to those warnings minimize the hazard?
5. Could an alternative, lower-risk design be used?
6. Given the identified risks of the product, do you, the manufacturer, consider the product to be reasonably safe?

Many products can be made safer through extensive design changes, but no product can be made foolproof and guaranteed as safe. The finesse is in determining whether the new product in question is safe enough for the market, based on the multifunctional analysis of risk. This, in turn, creates a risky situation for the product development team, so any decision should be reviewed and authorized by a level of management higher than the highest-ranking team member (risk analysis is discussed later in the book).

Product development is not just about FDA and sales revenues. It is first and foremost about the well-being of patients. Any medical product being developed must, of course, comply with applicable industry standards and regulatory requirements, and must not be demonstrably less safe than comparable competitive products (see Figure 5.3).

FDA approval of a product means that FDA believes that it is reasonably safe and effective for its labeled indications under its labeled conditions of use, but does not suggest an absence of risk. Rather, for purposes of marketing approval, FDA considers a product to be reasonably safe if the clinical significance and probability of beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has a positive benefit/risk balance on a population and individual patient level.

The fact that compliance with government and industry regulations, standards, or practice does not automatically result in a design being reasonably safe is never an excuse for lack of compliance. The failure to

1. The well-being of patients
2. Compliance with regulatory requirements
3. Compliance with applicable industry standards
4. Providing safety and efficacy not less than competitive products
5. Creating value for the company

Figure 5.3 Primary considerations for product development planning.

comply with FDA regulations is neither permissible, nor ethical, nor good business. So don't skimp on product testing or on risk analysis exercises, which are discussed elsewhere in this book. Both can reveal nonobvious product defects. Diligence in those processes can help to keep your company out of court.

Part II

Bringing a New Medical Product to Market

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6

Overview of the Approval Processes for Drugs, Biologics, and Medical Devices

In high art and in pure science detail is everything.

—Vladimir Nabokov

Now that the basics applicable to medical products and their regulation have been covered, it is time for a more detailed description of the actual process of product approval.

Product development planning encompasses the evaluation of product opportunities at all stages of development, of both internal and external origin. Too frequently, those who are responsible for regulatory and clinical activities for medical product manufacturers are excluded (willingly, unwillingly, or indifferently) from other areas of product development operations until someone determines that a new product is ready to be presented to FDA. This is unfortunate since even the most clever and productive scientists, marketing managers, and production managers will be thwarted if they don't have a realistic and fundamental concept of what is required for eventual approval or clearance for marketing. Without early regulatory and clinical involvement during product development planning, progress on developing a potentially valuable new product can come to a dead halt.

Significant consideration must be given to all regulatory and clinical pathways that remain before a product can be legally marketed, and if these requirements have been completed, to the strength and reliability of the information that has been generated. An intelligent assessment of time to market, cost to develop, and product use–associated risk requires an understanding of the regulatory road ahead. This chapter is especially targeted to those involved in product development who are not clinical or regulatory specialists.

DRUGS

Before a new drug can be marketed in the United States, it must receive approval from FDA's Center for Drug Evaluation and Research (CDER), based on data demonstrating that the drug is safe and effective for its intended use. For a new drug—especially for a new molecular entity (NME), which is an active drug substance that has never been previously approved by FDA—the journey from a gleam in a scientist's eye to FDA approval is arduous, long, costly, and complicated. There are a number of ways in which the approval of some products can be hastened. In addition to understanding the categorization of potential new products, those involved in product development planning should not overlook any possibility that a product is eligible for a more rapid review process. Conversely, care must be taken not to mistakenly assume that a product is eligible or to misunderstand just what is implied in pursuing one of the available options. These are options, and are not mandatory even if a product qualifies. The processes for fast-track designation, accelerated development, and priority review apply to products that would be a significant improvement in the treatment, diagnosis, or prevention of a serious or life-threatening disease. Each program carries its own risk, and manufacturers of this type of product need to examine all potential regulatory and clinical pathways.

Screening

The journey begins with laboratory investigations to identify possible candidate substances. Expert scientific and medical researchers try to conceptualize a target of action that might be effective in diagnosing, preventing, treating, or curing a disease. Thousands of compounds that have the potential of interacting with that biological target are screened in laboratory tests before a promising candidate substance is found. The candidates are extensively tested in preliminary laboratory studies to evaluate toxicity and pharmacologic effects. Most of the promising candidate drugs fall by the wayside because of obstacles encountered in these early steps.

Preclinical Testing

With few exceptions, new drugs must be shown to be safe and effective in human subjects before FDA approval can be considered (FDA can make exceptions to the clinical trial requirement for lifesaving drugs if testing in humans is unfeasible or unethical). The drug company must first convince FDA that the drug is reasonably safe to use in humans to evaluate safety

and efficacy in clinical trials. For a drug that does not have any history of clinical use, safety is established through preclinical (that is, nonhuman) laboratory testing, including testing in animals. FDA has guidelines and some regulations regarding the type of data and results it expects to see for a new drug before considering testing on humans, but the agency generally does not tell the drug company outright what specific laboratory evaluations or animal tests to run. As a result, the drug company often spends substantial time writing proposals and having discussions and meetings with FDA to identify a mutually acceptable preclinical program.

Preclinical testing can be very expensive. As discussed in Chapter 1, the complete capitalized preclinical program—also known as the "valley of death"—can cost up to hundreds of millions of dollars depending on the nature of the drug and on the availability of earlier safety and efficacy information. According to the NIH, 80 to 90% of research projects fail to make it through the preclinical stage, and industry statistics suggest that the number is even higher.[1]

Investigational New Drug Application

When preclinical testing satisfies the sponsor that the product is reasonably safe to move on to human trials, the company provides the data, along with manufacturing information and the proposed clinical protocol in an Investigational New Drug (IND) application, which is filed with FDA. The IND is essentially a request for permission to ship the new and as yet unapproved drug to the test site and to evaluate it in humans. If FDA agrees that the drug does not provide an unreasonable risk to humans, it allows the IND, and the company can proceed with clinical trials. It is estimated that only five in 5000–10,000 drug candidates that enter preclinical testing advance to human trials.[2]

Clinical Trials

The purpose of all of the investigations, studies, and FDA filings described above is to provide the foundation to justify that it is reasonably safe to test the new drug in humans in clinical trials designed to show the safety and effectiveness of the drug in the prevention, treatment, or cure of a disease. The results of the clinical trials are the most important factor in the ultimate approval or disapproval of a new drug. For drugs and biologics (see below), clinical trials generally comprise three preapproval phases, and often a post-approval phase, as illustrated in Figure 6.1. Clinical trials are discussed in greater detail in Chapter 11.

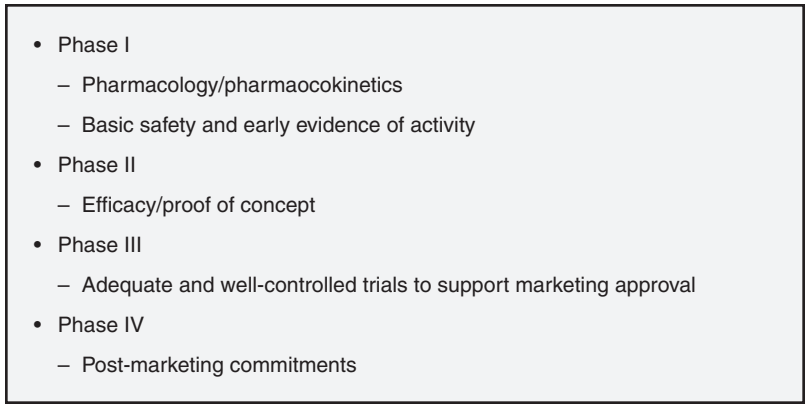

Figure 6.1 Phases of clinical testing.
Source: CDER.

New Drug Application

If the drug company determines that the data from the clinical trials successfully demonstrate the safety and efficacy of the new drug, a New Drug Application (NDA) is submitted to FDA. An NDA, which commonly will be 100,000 pages or more, contains all of the scientific information that the company has gathered on the drug; preclinical and clinical methods and results; statistical analyses of safety and efficacy data; detailed manufacturing information; information on packaging, stability, and labeling; patent information; and more. FDA reviews the NDA and ultimately makes a decision as to whether the drug is approvable or not. Before making the decision, the agency will usually call on an advisory committee of outside experts to seek a committee opinion on the approvability of the drug. The recommendations of an advisory committee are not binding, but the agency considers them very carefully when making approval decisions. Figure 6.2 shows the mean elapsed time from submission of the application for approval until FDA approval for priority (NME) drugs.

Drug manufacturers must pay a fee to FDA for review of NDA submissions, as stipulated by the Prescription Drug User Fee Act (PDUFA).[3]

Inspections

If all previous steps have been found acceptable, FDA inspects the manufacturing plant to assure itself that the company is manufacturing the drug in compliance with FDA's current good manufacturing practices (cGMP)

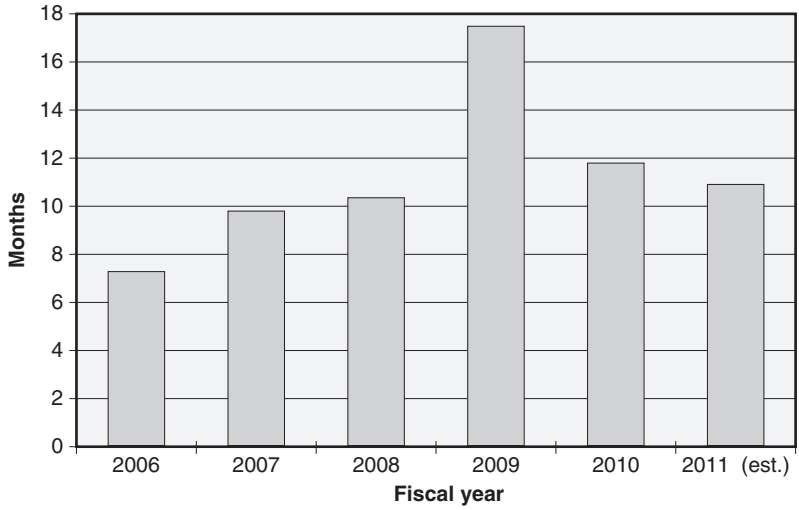

Figure 6.2 Mean time (months) from receipt to approval of priority NDA/BLA submissions.*

*Includes all submissions for NMEs, whether drug or biologic.

Source: FDA Justifications of Estimates for Appropriations Committees.

regulations. Assuming satisfactory results, FDA approves the drug for marketing in the United States.

Only five in 5000–10,000 compounds that enter preclinical testing will advance to human testing in clinical trials. Of those entering clinical trials, only one in five receive FDA approval for marketing. The total cost incurred by an innovator/pioneer drug company for discovering and developing a new drug is estimated to be over $1.3 billion, taking into account both out-of-pocket costs—investment income foregone as a result of research and development expenditures before any returns are realized—and costs of failed projects. The total time required for discovery and development of a new drug by an innovator/pioneer drug company has been estimated to be ten to fifteen years.

Generic Drugs and Abbreviated New Drug Applications

The first version of the drug product that is approved by FDA is known as an *innovator* or *pioneer drug.* A generic drug is comparable to an innovator drug in dosage form, strength, route of administration, quality, performance

characteristics, and intended use. There are specific patent-related issues that apply to the approval and marketing of generic drugs.

Generic drug manufacturers submit an Abbreviated New Drug Application (ANDA) to the Office of Generic Drugs at the CDER. These applications are called "abbreviated" because the generic drug manufacturers are not required to include preclinical or clinical data to establish safety and effectiveness, since those attributes were already established by the manufacturer of the innovator drug through the NDA process. Rather, an ANDA must provide information and data demonstrating that the drug product is bioequivalent to the innovator drug and that the proposed use and labeling is identical to that of the reference innovator drug, except for differences based on such things as manufacturer identity, tablet size or shape, distributor, and so on. Generic drug manufacturing plants are subject to the same inspection requirements that apply to manufacturers of new innovator drugs. Generic drug manufacturers do not pay PDUFA fees for review of ANDAs. In 2011, the estimated median approval time for original ANDAs was 26.7 months.[4]

BIOLOGICS

The clinical development and approval process for therapeutic biologics follows the same general pathway as for drugs. A sponsor who wishes to begin clinical trials on a biological product must submit an IND to FDA. Because biologics are derived from living organisms, and therefore are particularly at risk for immunogenicity, the IND will include information about the product's ability to elicit a protective immune response in animal testing. There also may be issues related to exclusion, destruction, or inactivation of pathogens that have the potential of being present in the source organism, organ, tissue, and so on. Rather than submitting an NDA, a biologics manufacturer files a Biologics License Application (BLA) for review and, with luck, for approval to market the new biologic.

Biosimilar Products (Follow-On Biologics)

In 2010, the comprehensive Patient Protection and Affordable Care Act (PPACA) was signed into law. The PPACA amends the PHS Act to create an abbreviated approval pathway for biological products that are demonstrated to be "highly similar" (biosimilar) to or "interchangeable" with an FDA-approved biological product. These new statutory provisions include specific aspects dealing with biosimilars as set forth in the Biologics Price

Competition and Innovation Act of 2009 (BPCI Act). Although U.S. legislation uses the term "biosimilars," it is not uncommon to see "follow-on biologics," "biogenerics," or "biocomparables" used in the same context.

Highly similar means that data must show that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. *Interchangeable* means that data must show that the biosimilar product can be expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing healthcare provider.

The new abbreviated regulatory pathway authorized by the PPACA is intended to be analogous to FDA's authority for approving generic drugs. However, in contrast to drugs, which are generally synthesized via a chemical process and are chemically well characterized, most biologics are complex substances for which complete chemical characterization is not possible. Biosimilars are rarely bioidenticals.

There are many scientific and legal considerations yet to be sorted out with regard to biosimilars, such as:

- Preclinical and clinical testing requirements
- Manufacturing processes
- Patent issues related to both the reference biologic and biosimilar
- Degree of product complexity suitable for an abbreviated approval pathway for biosimilars

It is likely that FDA will publish proposed guidance documents to allow public and industry input into any final regulatory recommendations.

MEDICAL DEVICES

As we have seen, although there is a legal distinction between drugs and therapeutic biologics, there is far more commonality than difference both within and between the product groups, and with regard to the FDA approval process. The category of medical devices, by comparison, includes an incredible variety of instruments, machines, supplies, devices, reagents, software, and other substances (some of which are themselves

biologics) that often seem to have little in common. Although FDA recognizes about 1700 general categories of medical devices (which are grouped into 16 medical specialties known as panels, see Figure 6.3), there are thousands of products comprising iterations and combinations of these device types. More than 10,000 U.S. manufacturers of medical devices are listed by the CDRH. Not surprisingly, the regulation of medical devices is not at all straightforward.

Medical devices that were marketed before the Medical Device Amendments to the FD&C Act was signed into law in 1976 are referred to as *preamendment* devices. The amendments required all devices to be classified into one of three device classes based on the extent of control necessary to provide reasonable assurance of safety and effectiveness.

Theoretically, device classification depends on the intended use of the device as well as the indications for use. In general, medical device classification is related to the risk posed by the device. Class I devices present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. About 47% of medical devices are Class I, about 43% are Class II, and about 10% are Class III.

In brief, the types of regulatory controls to which each class is subject are:

- Class I—General Controls
  - With exemptions
  - Without exemptions

Anesthesiology	Hematology and Pathology
Cardiovascular	Immunology and Microbiology
Clinical Chemistry and Clinical Toxicology	Neurology
Dental	Obstetrical and Gynecological
Ear, Nose, and Throat	Ophthalmic
Gastroenterology and Urology	Orthopedic
General and Plastic Surgery	Physical Medicine
General Hospital and Personal Use	Radiology

Figure 6.3 Medical device classification panels.
Source: CDRH *Device Advice.*

- Class II—General Controls and Special Controls
  - With exemptions
  - Without exemptions
- Class III—General Controls and premarket approval

The lack of obviousness in device classification is apparent to the industry and, to some extent at least, to FDA. In recent years, many devices have been reclassified by CDRH, and many devices have been exempted from certain requirements. Generally, reclassification has moved devices from a higher to a lower class, but there are a few exceptions. The only way to be sure of what's going on with class rank at a specific time is to check with FDA.

General Controls

You will notice that General Controls are requirements that apply to devices in all three classes. As such, they can be considered as the minimum requirements for medical devices. Unless specifically exempted by regulation, General Controls, in essence, require device manufacturers to:

1. Register each manufacturing location
2. List all marketed medical devices
3. Manufacture devices in accordance with current good manufacturing practices (cGMP) regulations
4. Label devices in accordance with applicable regulations
5. Submit a Premarket Notification [510(k)] unless the device is exempt from premarket notification or if it is identified as being subject to other requirements

In recent years, 95% of Class I devices and some Class II devices have been exempted from premarket notification and/or cGMP requirements. Up-to-date information from FDA must be reviewed before a regulatory pathway for a new product is determined.

While General Controls apply to all three classes of medical devices, they are the only level of controls that apply to Class I devices. Class I devices are subject to the least regulatory control because they present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices.

Class I devices are *not* intended to be:

- For use in supporting or sustaining life
- Of importance in preventing impairment to human life, and may not
- Present a potential unreasonable risk of illness or injury

Examples of Class I devices are elastic bandages, dental burs, tongue depressors, examination gloves, and the ever-popular enema kits. Most Class I devices are now exempt from the premarket notification and/or GMP regulation. However, FDA believes that some Class I devices will remain subject to premarket notification requirements, that is, require 510(k) filing. Based on FDAMA provisions, a Class I device is exempt from the premarket notification requirements under section 510(k) of the act unless the device is intended for a use that is of substantial importance in preventing impairment of human health or it presents a potential unreasonable risk of illness or injury (referred to as "reserved criteria"). FDA has evaluated all Class I devices to determine which device types should still be subject to premarket notification requirements. Examples of the so-called "reserved" Class I devices, which require premarket notification, are shown in Figure 6.4.

Special Controls

Special Controls apply to Class II medical devices. Class II devices are those for which General Controls alone are not adequate to assure the safety and effectiveness of a device, based on the potential of risk to health posed by the device. Special Controls will vary from product to product, but may include special labeling requirements, conformance with certain FDA guidances and mandatory performance standards, human clinical trials, and post-market surveillance.

Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes. A few Class II devices are exempt from the premarket notification requirement.

In Vitro Diagnostic Products (IVD). IVDs are reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. They are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVDs are medical devices, and may contain biological products. FDA classifies IVDs as Class I, II, or III according to the level of regulatory control that is necessary to ensure safety and effectiveness. The classification of an IVD, as with any other medical device, determines the appropriate

- Ammonia test system
- Bilirubin (total and unbound) in the neonate test system
- Iron (non-heme) test system
- Iron-binding capacity test system
- Magnesium test system
- Phosphorous (inorganic) test system
- Testosterone test system
- Uric acid test system
- Antimony test system
- Arsenic test system
- Carbon monoxide test system
- Cholinesterase test system
- Mercury test system
- Adenosine triphosphate release assay
- Russell viper venom reagent
- Blood bank supplies
- Vacuum-assisted blood collection system
- Transport culture medium
- Microbiological specimen collection and transport device
- Campylobacter fetus serological reagents
- Chlamydia serological reagents
- Epstein-Barr virus serological reagents
- Mycobacterium tuberculosis immunofluorescent reagents
- Trypanosoma spp. serological reagents
- Dental handpiece and accessories
- Boiling water sterilizer
- Surgeon's glove
- Pediatric position holder
- Patient examination glove
- Patient lubricant
- Protective restraint
- Ataxiagraph
- Electroencephalogram (EEG) signal spectrum analyzer
- Keratome
- Goniometer
- Mechanical wheelchair
- Scintillation (gamma) camera
- Positron camera

Figure 6.4 Examples of reserved Class I devices.
Source: Federal Register.

premarket process. As advances are made in personalized medicine, it has become quite common for new IVDs to be approved as companion tests intended to be used in conjunction with new drugs, to help ensure that the drugs will be used in the correct subpopulation of patients.

Premarket Notification

A small percentage of Class I devices, and most Class II devices, are cleared for commercial distribution or marketing through premarket notification,

also known as 510(k) clearance. The main concept behind 510(k) clearance is the assumption that the device being reviewed by FDA prior to its being marketed or distributed is substantially equivalent to one or more other devices already being sold in the United States. Specifically, the device must be regarded as substantially equivalent to a "predicate device," usually one marketed before the 1976 Medical Device Amendments (that is, a preamendment device); the predicate device can also be a post-amendment device that has already been found to be substantially equivalent to a preamendment device. FDA will find the new device equivalent if, after reviewing the submission, FDA is convinced that:

- The device performs the same function and falls within an established type of predicate device.
- The technological characteristics of the new device are comparable to the predicate device.
- Whatever differences in characteristics that do exist between the new and predicate device don't raise any new safety and effectiveness questions.

The premarket notification process has come under intense criticism.

There are concerns among some policymakers and patients about the ability of the 510(k) process to ensure that medical devices on the market are safe and effective. Others, as well as the medical device industry, regard the process as too burdensome and time-consuming and believe that it delays important new medical devices from entering the market. At the request of FDA, the Institute of Medicine (IOM) of the National Academies appointed a committee to review the 510(k) process and answer two questions:

- Does the current 510(k) process protect patients optimally and promote innovation in support of public health?
- If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) process optimally?

The IOM committee concluded that 510(k) clearance is not a reliable determination that the cleared device is safe or effective, that the premarket notification process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate-risk devices, and, furthermore, that it can not be transformed into one. The committee recommended that rather than continuing to modify the 510(k) process, FDA should direct its efforts at developing a science- and risk-based regulatory framework for

medical devices.[5] Whether this opinion will lead to any changes remains to be seen.

Premarket Approval

Premarket approval (PMA) is the required process of scientific review to ensure the safety and effectiveness of most Class III devices for which insufficient information exists to ensure safety and effectiveness solely through General or Special Controls. An approved PMA application is, in effect, a private license granted to the applicant to market a particular medical device. It is similar in spirit to an NDA or BLA, and securing PMA approval for a new Class III medical device can sometimes be as rigorous as securing approval for a new pharmaceutical.

Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Examples of class III devices that require a premarket approval include replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators. Based on certain complicated regulatory provisions, some Class III devices can be marketed with a Premarket Notification 510(k).

Class III devices generally need clinical evaluations, which are included in the PMA along with all other data involving safety, effectiveness, GMPs, and so on. PMA submissions are subjected to rigorous scientific review by both FDA personnel and an advisory committee representing the appropriate medical field. The requirements for PMA approval, like those for NDA and PLA approval, are very stringent.

Submissions to FDA for 510(k)s and PMAs can range from relatively simple and straightforward to extremely complex. FDA, of course, provides guidelines for preparing the required documents, but there is no boilerplate form.

The review of 510(k) submissions is supposed to be completed within 90 days, but that is often not the case. The mean total elapsed review time for 510(k)s increased to 140 days in fiscal year 2010 from 99 days in fiscal year 2006.[6] The situation is more time-consuming for PMAs. The total elapsed time from PMA submission to decision has been hovering around 300 days.

The product group that comprises drugs, biologics, and medical devices is large, complicated, diverse, and often unwieldy. A key to successful medical product development is to thoroughly understand what is required by regulations for a particular new product, what is not required but likely to be expected or recommended by FDA, and what is unnecessary

or unwanted. Good rapport with the reviewing group at FDA makes agreement on these issues much more likely. Really knowing your technology and product—how it is used, who will use it, what it does—and viewing FDA as an overworked organization with enormous responsibility, rather than as an adversary, will make life easier and allow new products to be reviewed and approved more quickly.

7
Quality by Design

No, Watson, this was not done by accident, but by design.

—Sherlock Holmes (A. Conan Doyle)

Volumes have been written about the value of TQM and tools such as *quality function deployment* (QFD), which is a structured approach to defining customer needs or requirements and translating them into specific plans to produce products to meet those needs. In the arena of healthcare products, there is no debate: applying quality principles to all company endeavors and deploying quality measures to ensure that customer requirements are coupled with product design are more than good ideas—they are requirements, and they are here to stay. Without documentation of the existence of quality processes and the verification that the processes are executed during product development, new healthcare products will not gain approval in the United States or be able to be sold in major overseas markets.

Medical product manufacturers are accustomed to establishing and following quality systems to help ensure that their products consistently meet specifications. Federal regulations specify that drugs and devices be manufactured in accordance with current good manufacturing practice (cGMP or GMP). GMP language is broad enough to describe minimum requirements for the methods, facilities, and controls used in the manufacturing, processing, packaging, and holding of products. GMP regulations for medical products do not prescribe in detail how a manufacturer must proceed as it designs and manufactures a specific product. Instead, a framework is presented requiring the manufacturer to develop and follow procedures and to fill in the appropriate details for a particular drug, biologic, or device. The upside of this umbrella approach is that it allows flexibility; the downside is that it can be sufficiently vague to risk not getting it right (in the eyes of

FDA, that is). However, the most important philosophy behind GMPs is that *quality must be designed and built into a product*. If you're involved in medical product development, this must become a way of life.

Current GMP requirements now cover a full quality systems approach and should be regarded as quality system regulation. Indeed, device GMPs are known as Quality System Regulations (QSRs). The new terminology emphasizing quality is facilitating the harmonization of FDA requirements with international standards. FDA notes that the quality requirements—which also apply to product design and development—embodied in the revised regulations have been accepted worldwide as necessary to ensure that acceptable products are produced. This opinion is contested by some in industry who point out that certain FDA requirements, for example in preclinical safety testing and in record-keeping requirements, may exceed those specified by international directives.

DESIGN CONTROLS

Historically, in the development of medical devices the process of design has been regarded as taking on more significance than it does in the development of pharmaceuticals. Devices have special challenges with regard to materials selection, three-dimensional conformation, and such things as physical, mechanical, electrical, and chemical functionality. The Safe Medical Devices Act (SMDA) of 1990 introduced a new element into medical device product development: it gave FDA the authority to add preproduction design validation controls to the GMP regulations. While the resulting quality-focused design controls were crafted for medical devices, the principles and objectives of design controls are equally important to drugs, biologics, and obviously to combination products: to make safe and effective products that conform to defined user needs and intended uses. By reviewing the design controls requirements for medical devices, the applicability and value of certain elements to other medical product categories should become clear.

The design phase is the most important development stage with regard to the effect on the life cycle of a device. It is at the design stage that the inherent safety, effectiveness, and reliability of a device are established. No matter how perfect a manufacturing process is, if the device doesn't have the qualities of safety, effectiveness, usability, and reliability designed into it, it isn't going to do what it's supposed to do the way it's supposed to do it. Only careful planning, review, and management of the processes involved in product development can ensure that an acceptable product will be developed.

Design deficiencies are always costly and often dangerous. In an analysis of several years of medical device recalls, FDA determined that about 40% were attributable to design defects. In some cases, the original product design was faulty but was not detected until the product was in commercial use. In other cases, changes made to existing products—often in attempts to correct problems—produced new defects. In 1996, the U.S. Supreme Court unanimously ruled that consumers injured by certain medical devices because of faulty design can seek damages against the manufacturer under state law, even if the devices comply with FDA regulations.[1] The ruling applies to devices cleared through findings of substantial equivalence via 510(k) Premarket Notification.

Once a project has passed through the design stage, it has a greater probability of becoming a new product. Typically, bad designs are likely to become bad products. It is difficult and costly to reverse the process before a product is launched, and even more difficult and costly to undo the damage in the marketplace after a poorly designed product is introduced. The costs associated with providing bad products can include internal failure costs, that is, costs associated with defects found before the product makes it into the customers' hands; external failure costs, that is, costs associated with defects found after the customer receives the product; appraisal costs, that is, those incurred to determine quality issues leading to the problem; and prevention costs, to prevent a repeat occurrence.

Figure 7.1 illustrates the 1–10–100 rule, which summarizes the exponential relationship between the cost of correcting design defects and the stage of development.

The central philosophy of device GMPs as they affect product development is embraced in the concept of design controls.[2] In their essence, design

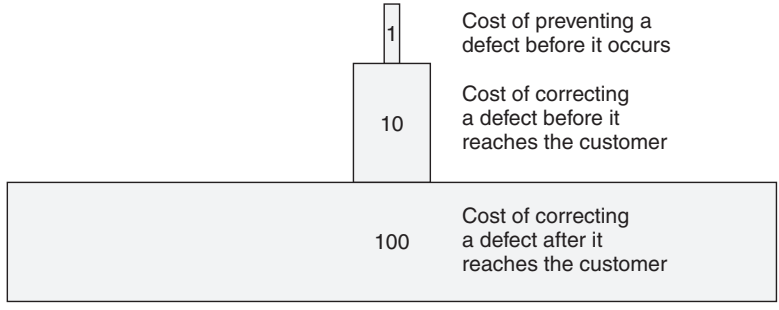

Figure 7.1 The 1–10–100 rule.

Source: C. Gevirtz, *Developing New Products with TQM* (New York: McGraw-Hill, 1994). Reproduced with permission of The McGraw-Hill Companies.

controls constitute a system to ensure that a new product that is eventually manufactured can be used safely and effectively while meeting customer needs. Design controls require manufacturers to establish and maintain formal controls for their product development activities. There must be a process that takes product design through a series of steps, from identification of product requirements and specifications through rigorous testing and validation. In other words, the seat-of-the-pants system of product development that had even recently been common in companies both large and small is gone for good.

A significant challenge for anyone working in product development in the healthcare field, especially with medical devices where stringent controls and requirements are a relatively new issue, is overcoming a bad attitude. Having to do all of the things required by design controls is unfamiliar and unpleasant to many of the people involved in product development. Marketing people and scientists seem to be hit the hardest. Management also tends to be nonsupportive, unappreciative of the global impact of noncompliance, and is often critical of the perceived extra costs, delays, and human resource drains. In reality, there are still many medical device manufacturers that either knowingly or unwittingly ignore design controls.

Some few optimistic and progressive manufacturers actually regard design controls as an opportunity to improve their product development process. Many more, bridling at what they regard as yet another burden unjustifiably thrust upon them, continue to rant, resist, and protest. Others regard the new requirements as a necessary evil, and not unexpected in light of the evolving harmonization of international requirements for the marketing of medical devices. The point is that quality regulations are not going to go away, and those responsible for healthcare product development will have to lead the charge to keep up the momentum in their organizations.

Requirements for design controls are not intended to apply to the very early stages of product development, such as research, review of ideas, formulation of concepts, or preliminary feasibility studies. However, once it is decided that a design will be developed, a plan must be put into effect that will establish the adequacy of the design requirements and ensure that the design meets all of the agreed-on requirements before production.

Design controls are based on quality assurance and engineering principles. Design controls implementation is required by FDA for Class II and Class III devices, and for some Class I devices (see Figure 7.2), including those automated by computer software. Combination products requiring interaction between devices and drugs or biologics also require application of design controls.

Because design controls must apply to a wide variety of devices and combination products, FDA regulations do not specify the practices that

Catheter, tracheobronchial suction

Glove, surgeon's

Restraint, protective

System, applicator, radionuclide, manual

Source, radionuclide teletherapy

Devices automated with computer software

Figure 7.2 Class I devices subject to design controls.

must be used, but instead establish a framework for manufacturers. The framework provides manufacturers with the flexibility needed to develop design controls that are most appropriate for their own design and development processes while complying with regulations.

The regulations require each manufacturer to establish and maintain procedures for the following:

- Design and development planning
- Design input
- Design output
- Design review
- Design verification and validation
- Design transfer
- Design changes
- Design history file

A very stripped-down look at each element will help to set the stage for creating an integrative product development process that will be compatible with the organization and structure of a device manufacturer, meet FDA requirements, facilitate securing permission to market internationally, and—best of all—expedite the development of new, high-quality products.

Design and Development Planning

This requires that a plan be created to describe the activities necessary to design and develop the specific product and to define responsibility for its implementation. Interfaces among and between individuals, groups, and activities should be identified and described. For many new devices

and associated manufacturing processes that use software, these tasks are further complicated because of the importance of software, and the possibility of subtle software errors. This stage is when the following questions should be considered:

- What is going to be done?
- Who is going to make sure it gets done?
- Who is going to do it?
- When will it all happen?

Figure 7.3 indicates the kinds of items that might be included in a checklist for putting together a plan for design controls.

- User/patient requirements
- Physical characteristics and constraints of the device
- Regulatory and voluntary standards requirements
- Safety needs of the user
- Type of failure mode analysis
- Anticipated possible misuse of the device
- Elimination or minimization of user-related failures
- Need for fail-safe characteristics
- Producibility of the design
- Functional requirements
- Environmental requirements
- Test requirements: physical, chemical, biological, safety, efficacy
- Maximum and minimum tolerances
- Acceptance criteria
- Components selection
- Packaging requirements
- Sterilization method and requirements
- Labeling and instructions
- Shelf-life and storage requirements
- Serviceability and maintainability

Figure 7.3 Examples of items to include in a design controls checklist.

Design Input

Design input includes all of the steps necessary to ensure that the design requirements for a specific device are appropriate, address the intended use of the device, and meet the needs of both the user and the patient. It is the starting point for product design. In this stage, information is gathered about performance requirements, engineering requirements, regulatory requirements, and applicable standards. Preliminary specifications for elements such as design characteristics, form and configuration, and materials are also defined during this stage.

The design input phase should be viewed as a cross-functional continuum because intensive and formal input requirement activities usually occur near the beginning of the feasibility phase and continue into the early physical design activities. Once the concept of the new device design is established, these basic questions should be answered:

- What is the real need for the new device?
- Where will the new device be used?
- Who will use the new device?
- How will the new device be used?
- With what other devices will the new device be used?
- How long will the new device be used?
- Other questions related to the specific device to be developed.

Design Output

This is made up of the product and process documentation that is used to transform a product idea into a prototype or finished product. It must also include the test plans, procedures, and reports that will verify that a product meets the design input requirements. The records and results of each design phase make up the design output. The nature and number of design phases is determined by the manufacturer.

The following three activities are regulatory requirements for design output:

1. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements.

2. Design output procedures shall contain or make reference to acceptance criteria and ensure that those design outputs that are essential for the proper functioning of the device are identified.
3. Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.

Design Review

Design review is a formal and documented procedure for assessing design results, and is to be conducted at appropriate stages of the product development process. The design review is intended to ensure that the design of the product being developed conforms to the established criteria, and to identify design deficiencies or defects. Reviews are supposed to be unbiased and objective examinations by appropriately trained individuals who do not have direct responsibility for design development. Thus, a key element for successful design review is the formal identification, designation, and utilization of independent participants. Device design and design reviews should progress through defined and planned phases starting with the design input phase and continuing through validation of initial production units or lots. Design review should be conducted by representatives of all functions that have been involved with the design stage being reviewed. How frequently reviews are conducted is up to the manufacturer, reflecting the organization's staging of the product development process.

Design Verification and Validation

This refers to a series of ongoing procedures that ensure that a product's design output meets its design input, and that the device conforms to defined user needs and intended uses. Specifically, *verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled, and *validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled. Risk analysis is especially important in this stage. Generally, testing of prototype (or sometimes of production) units must take place both under defined test conditions and under actual or simulated use conditions. Preclinical and clinical testing, failure analysis, and cost analysis are part of the program.

Design Transfer

Design transfer procedures ensure that the design basis for a device and its components is correctly translated into production specifications. It involves transferring all of the documentation from the design process to manufacturing. Of course, once the design is translated into physical form, FDA specifies that its technical adequacy, safety, and reliability should be verified through comprehensive documented testing under simulated or actual use conditions.

Design Changes

Design changes take place for various reasons. Each manufacturer must establish and maintain procedures for the identification, documentation, validation, verification, review, and approval of any design changes.

Design History File (DHF)

This is the name given to the compendium of all the records, or references to the records, that are necessary to demonstrate that the design of a specific product was developed in accordance with the approved design plan. For example, the results of all design reviews are included in the design history file.

OTHER CONSIDERATIONS IN DESIGN CONTROLS

FDA is rather adamant that failure mode analysis be conducted at the beginning of the design effort and as part of each design review. The objective is to identify potential design weaknesses and inadequacies that might adversely affect safety and performance, and to then take corrective action to remove or minimize the undesirable effects. There are a number of techniques to accomplish this, including *fault tree analysis* and *failure mode effects and criticality analysis.* Details of these techniques, which are also addressed in another chapter of this book, are available from various sources.[3] The important thing is that a systematic way to identify and address potential design weaknesses be used and documented.

Because design controls must apply to a wide variety of devices, the regulation does not prescribe the practices that must be used. Instead, it

establishes a framework that manufacturers must use when developing and implementing design controls. The framework provides manufacturers with the flexibility needed to develop design controls that both comply with the regulation and are most appropriate for their own design and development processes.

Manufacturers are free to develop and define the details of their own design control systems. They must, however, meet the general requirements of the GMP regulations. Everyone who works in healthcare product development must be committed to TQM, must be aware of the design control requirements in FDA regulations, and must comply with the company's approved design control system to ensure that the requirements are met. In fact, it should be the product development organization that creates the design control system.

8

Designing-Out Disaster: Risk Analysis

Risk comes from not knowing what you're doing.

—Warren Buffett

Try as one might, it is impossible to design and develop a product that is risk-free. This is especially true of medical products. Even in what might appear to be the best of all possible product development worlds—in which a design is flawless, the labeling perfect, and clinical trial results unassailable—elements beyond the control of the most astute product development team will conspire to introduce the potential of product-related hazard. Have no doubt: someone or something will spoil the broth.

Risks, of course, can lead to hazards. Any hazard is a potential source of harm, and medical products are associated with a dizzying array of hazards: biological hazards, chemical hazards, mechanical hazards, thermal hazards, electrical hazards, radiation hazards. There are hazards related to the use of a medical product, such as use in ways that are not anticipated by the manufacturer; use in ways that are anticipated but are inadequately controlled; requirements for proper use that exceed the physical, perceptual, or cognitive abilities of the user; nonintuitive use, that is, inconsistent with a user's expectations; dependency of proper use on a specific environment, when the effect of environment differences is not understood by the user or if proper use in specific environments exceeds the capacities of the user. Hazard is typically triggered by inherent risk of the product in medical treatment, product failure or malfunction, and the way the product is used. Sloppy, non-GMP manufacturing, undocumented and unreported changes made by suppliers of raw materials, inadequate quality control on the part of manufacturing equipment manufacturers, and slip-ups in the shipping, storage, and distribution chain are a just a few of the elements that can contribute to product hazard.

The challenges of reducing risk and hazard potential by making a product doctor-proof and patient-proof are well known to most product developers. The truth is, though, that regardless of whether a product has been demonstrated to be safe enough to gain FDA clearance or approval for marketing, there *will* be risk associated with its use.[1] In turn, "risk" is a relative term that has meaning only in the context of the benefit provided by the product. Risk and benefit, then, are subjective attributes, and at some point in product development a call must be made whether the benefit of a medical product sufficiently outweighs the risk attendant to the product. Misjudgment of product risk and benefit further contribute to potential product hazard, the result of which can be harm to patients, product recalls, and product liability lawsuits. Major sources of medical product risks are summarized below:

- Product defects
  - Design defects
  - Manufacturing defects
  - Warning defects
- Side effects
  - *Avoidable known side effects*: predictable reactions under certain improper conditions of use (usually clarified by product labeling)
  - *Unavoidable known side effects*: inherent physical or physiologic reactions that can be expected to occur even with proper product use
  - *Unknown side effects/consequences*:
    - Associated with long-term use
    - Associated with concurrent use of other products
    - Associated with off-label (unapproved or unstudied) uses
    - Associated with use in an unstudied patient population
- Use errors:
  - By healthcare professional
  - By patient
  - By caregiver

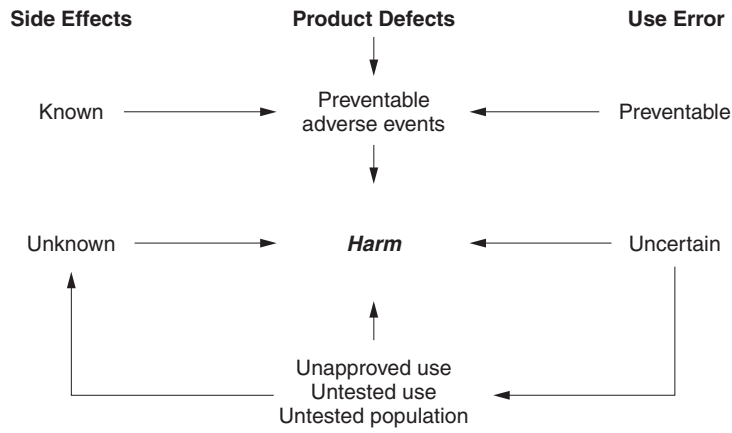

Figure 8.1 Examples of potential interactions of risk elements.

Potential interactions of these contributing risk elements are shown in Figure 8.1.

Risk assessment is the process of identifying, estimating, and evaluating the nature and severity of risks associated with a product. It is an important component of design controls, and is a process that should take place throughout a product's life cycle. To avoid problems during the later stages of product development or after product launch, it is important to have as good an idea as possible of the product's underlying risks and benefits prior to FDA approval or clearance for marketing.

While a product development team may have a vanishingly small or nonexistent role in the manufacturing, prescribing, dispensing, and ultimate use of a healthcare product, it does have considerable influence over design controls, development, testing, and labeling of a new medical device, biologic, or drug. Indeed, prudent pharmaceutical and medical device companies have begun to incorporate risk-reduction activities during the development phase.[2,3] Those involved in product development planning play a key role in providing the greatest possible assurance that the risk of a new product is as minimal as can be. They also should play a critical role in the determination of the extent to which the product's benefits are expected to outweigh its risks. If for some reason upper management does not recognize the ethical or business implications of minimizing risk, the personal liability they may face should a product prove to be hazardous for reasons that were identifiable and/or avoidable might get their attention.

QUALITY RISK MANAGEMENT

The importance of quality systems has long been recognized in the medical products industry. It has become increasingly evident that quality risk management is a valuable component of an effective quality system. *Quality risk management* can be thought of as a systematic process for the assessment, control, communication, and review of risks to the quality of the product across the product life cycle. Activities especially subject to quality risks include development, manufacturing, packaging and labeling, distribution, inspection, and review processes throughout the life cycle of the product. The guiding principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.[4]

The risk to quality, however, is just one component of the overall risk. Instituting a system for risk management as part of the product development process will facilitate understanding and addressing the factors relevant to the potential of a product to cause harm. This process can be tailored to the specific category and use of the new product, but at the very least should provide the means to accomplish the objectives shown in Figure 8.2. The evaluation of the risk should be based on scientific knowledge and hold the protection of the patient as the most important goal.

1. *Identify* the potential sources of risk in the product and with reasonably anticipated use of the product.
2. *Describe* how hazardous use situations occur.
3. *Analyze* the causes for identified failure modes and risk sources.
4. *Evaluate* the seriousness of risk and the severity of potential harm.
5. *Eliminate*, *correct*, *minimize*, or *accept* the defects or weaknesses by redesigning, reformulating, labeling, and so on.
6. *Reevaluate* risk/benefit based on the above.
7. *Document* the processes and findings.
8. *Communicate* findings and recommendations to other decision makers.

Figure 8.2 Objectives of risk assessment and management.

RISK ANALYSIS TECHNIQUES

Medical device manufacturers are more familiar with traditional methods of risk analysis because FDA's quality system regulation for medical devices requires risk analysis, where appropriate—that is, unless the manufacturer can document justification to the contrary. Since being an apologist is in itself risky, in reality, risk analysis is a must for a manufacturer to be able to make an ethical and business call on whether a new device is safe enough to market. Although not expressly required for FDA approval for drugs and biologics, the principles of risk analysis techniques are applicable to these products, and are key elements in risk management strategies for drugs and biologics, as well as for medical devices. A variety of risk analysis methods are used to determine malfunctions, or signs of malfunctioning, that appear either immediately before or immediately after the failure of a critical parameter in a product or system. These analysis methods, in various ways, identify:

- Accident scenarios: what could/did go wrong, and what is the probability of occurrence?
- Consequence scenarios: what are the possible outcomes, and how serious are they?

Failure mode analysis determines which malfunction symptoms appear immediately before or after a failure of a critical parameter in a system. After all the possible causes are listed for each symptom, the product is designed to eliminate the problems. *Failure mode and effects analysis* (FMEA) identifies potential design inadequacies that may adversely affect safety and performance. Each potential failure mode, including possible human-induced failures or unusual hazardous situations, is considered in light of its probability of occurrence. In the case of medical devices, and increasingly with drugs and biologics, two techniques are typically (but not exclusively) used: *fault tree analysis* (FTA) and *failure mode effects and criticality analysis* (FMECA).[5] Grossly simplified, FTA asks "what happened?" and provides the most likely answers, while FMECA asks "what could happen?" and provides the most likely answers.

FTA represents a deductive approach to failure mode analysis. It begins by assuming that a failure or safety hazard has occurred (*my printer doesn't work*) and works backward to identify the defects, conditions, interactions, and so on, that could lead to the failure (*the printer is not plugged in, the printer cable is damaged, the proper driver is not installed*). As a top-down approach, FTA is especially applicable to analysis of after-the-fact problems, when an unwanted event has already occurred.

FMECA is an inductive process that begins by identifying and assuming defects at a basic component level (*the printer is not plugged in, the printer cable is damaged, the proper driver is not installed*) and then determines the effects on higher system levels (*the printer won't work*). As a bottom-up approach that anticipates what could go wrong, FMECA is especially useful during the design and development stages of products. FMECA should be iterative to correspond with the nature of the specific design process.[6]

In addition to identifying potential failure modes, FMECA assigns a value to the severity of the effect and to how important the failure is to the safety of the device (criticality). A qualitative but numeric value is also assigned to the probability of occurrence of each identified failure mode. Often, a lower score is assigned to a higher degree of risk or probability. That is, if a failure mode can be expected to occur frequently, it might be assigned a value of 1, while a failure mode with a remote likelihood of occurrence might be given a 20. Ditto for the scoring of the seriousness or severity of the outcome of a failure event. To me, this approach is counterintuitive, and therefore subject to misinterpretation and misuse by all but seasoned risk analyzers. A more analyst-friendly approach is to assign a high number to a high likelihood of failure, and a low number to a low likelihood of failure, and a high number to a severe effect, and a low number to a mild effect.

There is no purpose in conducting risk analysis during product development or technology assessment if no one is able or willing to make the call on whether a product is safe enough. *Risk control* includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level, which means that an acceptable level of risk must be determined for every product and process. Factors such as cost/benefit benefit/cost may be used to facilitate making a call on the acceptability of risk and the optimal level of risk control. Risk control decisions and actions might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance between benefits, risks, and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Just as the exact format for FMECA can be customized to specific products, so must the definition and assignment of criticality factors and decision-making criteria be customized. For example, a risk score of 10 derived from some arbitrary FMECA protocol matrix might be absolutely unacceptable for a cardiovascular stent, but might be a good score for an artificial heart. The risk/benefit relationship has to be folded into the mix. So FMECA is simultaneously qualitative and quantitative, objective and subjective. Never back-fit a product into the matrix to obtain an acceptable score. A generic example of an FMECA scoring matrix is shown in Figure 8.3.

It is not always appropriate or necessary to use a formal risk management process. Informal risk management processes based on empirical tools and internal procedures can be considered acceptable. As already discussed, the level of effort, formality, and documentation of the risk management process should be commensurate with the level of risk.

When corners are cut in the identification, analysis, and minimization of risk, the cost can be adverse events, product recalls, and product liability litigation. Adapting and applying failure mode analysis methods to the product development planning process for all new medical products—whether the products are being developed internally or acquired from an external source—will enhance the quality techniques that lead to safe and effective medical devices, drugs, and biologics.

Component or function	Failure mode	Effect caused by failure	Probability of failure[1]	Severity of effect[2]	Criticality score[3]	User detection means	Corrective action/ applicable controls

[1] Probability of occurrence of failure:
Remote = 1
Unlikely = 2
Occasional = 3
Frequent = 4

[2] Severity of effect of failure
Minor (no injury; product function not affected) = 1
Moderate (temporary illness or injury or product failure) = 4
Major (injury or illness requiring intervention; definite product failure) = 7
Critical (permanent injury or illness, requiring extensive intervention) = 10
Catastrophic (death or major permanent disability) = 15

[3] Probability × Severity

Figure 8.3 Example of FMECA matrix.

9

Recalls, Withdrawals, and Revocations

We place absolute confidence in the Titanic. We believe the boat is unsinkable.

—Philip A. S. Franklin,
Vice President, White Star Lines

For medical products manufacturers, the cost of compliance with FDA regulations is high. Strict adherence to the principles of good product development, good clinical practices, good manufacturing practices, post-marketing surveillance, and other must-do tasks requires time, money, and effective human effort. The price, though, represents a sound investment considering that the cost of noncompliance can quickly eclipse the cost of compliance. For reasons that may be unintentional or intentional, unforeseeable or readily foreseen, products sometimes don't meet standards and expectations related to such considerations as manufacturing, performance, or safety—which can lead to a temporary or permanent removal of the product from the marketplace. In mid-2003, FDA announced that it would step up enforcement actions, which included removing products from the market.[1]

RECALLS

A *recall* is a firm's removal or correction of a marketed product, including its labeling and/or promotional materials, that FDA considers to be in violation of the laws it administers, and against which the agency could initiate legal action (for example, seizure or the full range of administrative and civil actions available to the agency). A product recall is not a remedial action; it is the cost of failure, which is frequently the consequence of noncompliance.

Recalls can be implemented through several different actions. They may be voluntary, semi-voluntary, or ordered by FDA.[2]

Firm-Initiated Recalls

A manufacturer or distributor may voluntarily initiate a recall at any time. The firm must notify FDA of the recall, and FDA will classify the recall depending on the risk that the violative product poses, and will monitor the recall process.

FDA-Requested Recalls

Under certain urgent situations, FDA may request that a manufacturer or distributor recall a product. An FDA request that a firm recall a product is ordinarily reserved for urgent situations. The recall is still regarded as voluntary on the part of the responsible firm. However, if the company fails to acquiesce, the recall will become statutory, that is, a result of FDA obtaining a court order authorizing U.S. marshals to seize the product because the manufacturer refuses to see the light.

FDA-Ordered Recalls

Under certain authorities, FDA may mandate a recall. FDA does not mandate recalls of drugs except via the statutory actions described above, although there has been congressional and public pressure to grant FDA such authority. FDA does, however, have mandated recall authority for unsafe biological products, human tissues, medical devices, and certain other products. In the context of a mandatory recall, those conditions in the relevant guidances, statutes, and/or regulations are requirements rather than recommendations. That is, they are not voluntary.

FDA classifies recalls into one of three classes to indicate the relative degree of health hazard presented by the product being recalled:

- *Class I* is a situation in which there is a reasonable probability (strong likelihood) that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- *Class II* is a situation in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

- *Class III* is a situation in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.

Many less-serious voluntary recalls involve only specific lots, batches, or manufacturing runs, and the manufacturer can continue to market the product except for the specifically recalled examples. Such recalls often involve out-of-specification products resulting from temporary and solvable problems in manufacturing, storage, or shipment. The recalled products are usually destroyed, but in some cases they can be reconditioned to comply with FDA regulations. Manufacturers usually carry out their responsibilities to protect the public health by voluntarily recalling products that are defective or present a risk of injury to consumers.

WITHDRAWALS

Recalls do not include a firm's market withdrawal or a stock recovery. A *market withdrawal* is a manufacturer's removal or correction of a distributed product either for a minor violation for which FDA would not normally initiate legal action, or for certain reasons that do not involve a violation at all (for example, normal stock rotation practices, routine equipment adjustments and repairs, product improvements). The removal of medical products from the market as a result of actual or alleged tampering is also considered a market withdrawal, even in the absence of manufacturing or distribution problems.

A *safety-based withdrawal*, however, is a complete cessation of the marketing of a drug or device because of an intrinsic property of the drug or device that poses serious safety concerns. Generally, this means that the approval of the product is withdrawn.

REVOCATIONS

A *revocation* is the cancellation of a license for a biological product and of the authorization to ship a biological product for sale, barter, or exchange in interstate commerce. A revocation may occur either at the request of the manufacturer or when grounds exist for FDA to initiate such an action.

The removal of products by recall, withdrawal, or revocation almost always applies to products that have already been cleared or approved for marketing and that have already been launched to the market. FDA on

occasion withdraws approval of an IND or IDE for a product being evaluated in clinical trials if there are serious safety concerns. As someone involved in product development planning, and not involved with manufacturing or marketing, you might think that you're off the hook with regard to recalls, withdrawals, and revocations. Not so. While some market removals result from completely unpredictable causes (for example, consumer tampering of a drug or device) or the appearance of new diseases that could affect the safety of source materials for certain biologics (for example, blood donors who later develop variant Creutzfeldt-Jakob disease), most do not. It is not uncommon to have warning signs crop up, but not be appropriately addressed, during various stages of product development

Although it might take years for the adverse effects of a new drug, biologic, or device to be observed, this is not always the case, as can be seen in Table 9.1.

Device companies have historically been less compliant with FDA regulations than drug companies, and the incidence of device recalls, as a percentage of products marketed, is greater than the incidence of drug recalls (see Figures 9.1 and 9.2). Biologics products account for far more recalls than drugs, and have the greatest number of recall actions in terms of the number of recalls as a percentage of products marketed (see Figure 9.3).[3]

Table 9.1 Examples of safety-based withdrawals of product approvals.

Trade name	Product type	Use	Year approved	Year withdrawn
Darvocet/ Darvon	Drug	Pain management	1957	2010
Meridia	Drug	Weight loss	1997	2010
Mylotarg	Drug	Leukemia treatment	2000	2010
Octagam	Biologic	Primary immune deficiency	2004	2010
Raptiva	Drug	Plaque psoriasis treatment	2003	2009
Bextra	Drug	Pain relief	2001	2005
Cylert	Drug	Attention deficit hyperactivity disorder	1975	2005
Vioxx	Drug	Pain relief	2002	2004
Intergel	Device	Surgical adhesion prevention	2002	2003

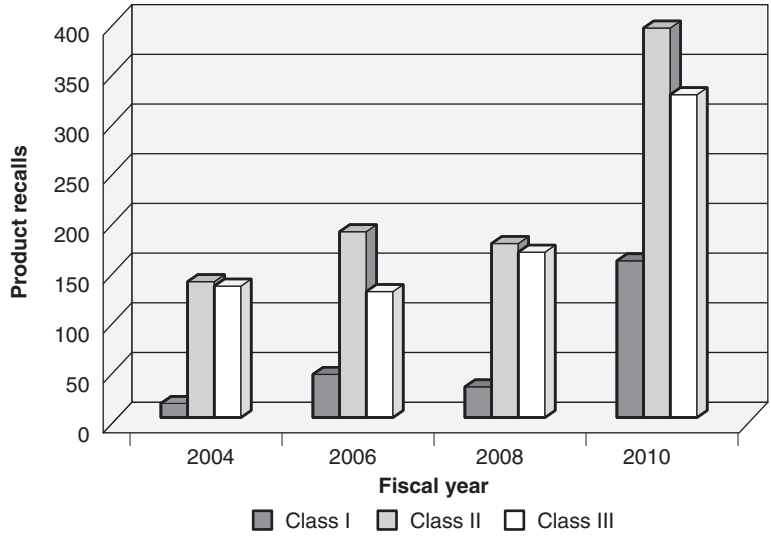

Figure 9.1 CDER recall statistics.

Source: FDA Division of Compliance Management and Operations, Office of Enforcement.

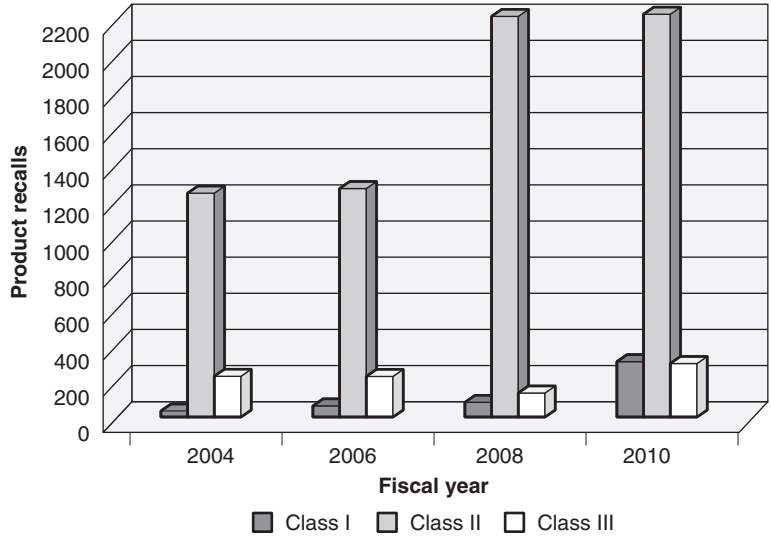

Figure 9.2 CDRH recall statistics.

Source: FDA Division of Compliance Management and Operations, Office of Enforcement.

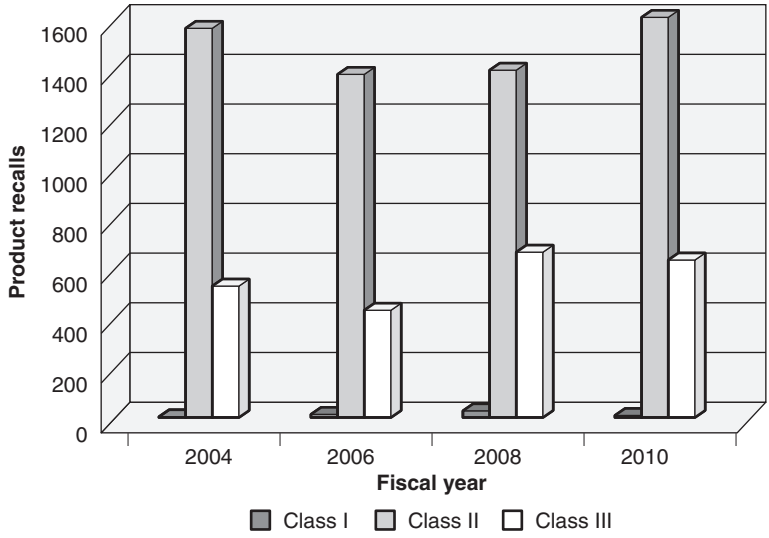

Figure 9.3 CBER recall statistics.

Source: FDA Division of Compliance Management and Operations, Office of Enforcement.

INFLUENCE OF PRODUCT DEVELOPMENT PLANNING

There are measures that can be taken during product development planning that can reduce the likelihood of a product being the subject of a recall. Important questions that should be addressed and readdressed during new product planning and development phases include:

- Is there confidence that the manufacturing entity—whether internal or contracted—can and will manufacture the product consistently and reliably according to cGMP requirements?
- Is the product's target population clearly defined?
- Does the product carry a high probability of being used outside of the target patient population?
  - If yes, is there a reasonably foreseeable safety risk associated with the use of the product in other groups?

  - If yes, can labeling, education, and surveillance reduce the risk?
- Have clinical trials adequately examined the safety and efficacy of the product in a reasonably representative target population?
- Is the product designed so that its intended use is intuitive?
  - If no, can labeling and education clearly describe intended use?
- Is the product designed so that its application or administration is intuitive?
  - If no, can labeling and education clearly and effectively convey instructions?
- Is the safety profile of each individual component or ingredient of the product known?
- Is there previous knowledge of the interactions of the component materials or ingredients?
- Have the principles and requirements of design controls been implemented for products that are medical devices?
- Has a rigorous risk analysis been conducted to identify and quantify the hazards of product failure and product misuse?

No one can make a product that is foolproof or that will be safe and effective for each and every patient who will ever be exposed to it. Keeping the patients and the users of the products foremost in mind during development or acquisition of a new product will bring you a little closer to that unattainable goal.

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10

Human Factors and Usability Engineering

Minimizing Medical Errors

Everything should be made as simple as possible, but not simpler.

—Albert Einstein

It is highly likely that at some time in your life you have encountered a product that you regarded as difficult, if not impossible, to use. Perhaps the problem related to a package that defied opening, or a difficult-to-read label that didn't provide the information needed. Perhaps the product was awkward to maneuver, or its regular use resulted in a repetitive stress injury. Such encounters often lead to dissatisfaction with a product or even to misuse of a product. When the paths of a human being and some healthcare technology cross, an extensive array of critical interactions takes place. These interactions occur whether the technology involves a product that falls into the category of drug, biologic, or medical device; and these interactions occur regardless of whether the human is the individual purchasing the product, using the product, or upon whom the product is used. The discipline that seeks to analyze and optimize the relationship between human beings and any technology is known as *human factors*.

Human factors is the study of how people use technology. It involves the interaction of human abilities, expectations, and limitations with work environments and system design. *Human factors engineering* is the application of human factors principles to the design of devices and systems. The term *human factors engineering* is often used interchangeably with the terms *human engineering*, *usability engineering*, or *ergonomics*. In the context of medical product applications, human factors engineering helps improve human performance and reduce risk. Table 10.1 shows a suggested format for providing human factors engineering and usability engineering information to FDA for device submissions.

Table 10.1 Outline of device HFE/UE report.

Sec.	Contents
1	Intended device users, uses, use environments, and training • Intended user population(s) and critical differences in capabilities between multiple user populations • Intended uses and operational contexts of use • Use environments and key considerations • Training intended for users and provided to test participants
2	Device user interface • Graphical depiction (drawing or photograph) of device user interface • Verbal description of device user interface
3	Summary of known use problems • Known problems with previous models • Known problems with similar devices • Design modifications implemented in response to user difficulties
4	User task selection, characterization, and prioritization • Risk analysis methods • Use-related hazardous situation and risk summary • Critical tasks identified and included in HFE/UE validation tests
5	Summary of formative evaluations • Evaluation methods • Key results and design modifications implemented • Key findings that informed the HFE/UE validation testing protocol
6	Validation testing • Rationale for test type selected (that is, simulated use or clinical evaluation) • Number and type of test participants and rationale for how they represent the intended user populations • Test goals, critical tasks, and use scenarios studied • Technique for capturing unanticipated use errors • Definition of performance failures • Test results: Number of device uses, success and failure occurrences

Continued

Table 10.1 *Continued.*

Sec.	Contents
	• Subjective assessment by test participants of any critical task failures and difficulties • Description and analysis of all task failures, implications for additional risk mitigation
7	Conclusion The <Name Model> has been found to be reasonably safe and effective for the intended users, uses, and use environments. • The methods and results described in the preceding sections support this conclusion. • Any residual risk that remains after the validation testing would not be further reduced by modifications of design of the user interface (including any accessories and the IFU), is not needed, and is outweighed by the benefits that may be derived from the device's use.

In recent years, FDA has exhibited a growing interest in human factors. The driving force in this interest was the realization by the agency that use-error is a significant cause of patient morbidity and mortality. FDA now wants manufacturers of medical devices to pay attention to human factors early in the product development process to catch and correct problems related to interfaces before a healthcare product reaches the market.[1] For example, FDA expects human factors studies to be encompassed in the user interface design and validation activities of the design controls requirements included in the current revised quality systems regulations (that is, GMPs) for medical devices (Figure 10.1 summarizes the CDRH definition and benefits of human factors in medical device design). In other words, a device manufacturer will be required to document that human factors were considered in the process of design development.[2] To assist industry in fulfilling this requirement, FDA has formed a human factors engineering team at CDRH, and has issued a number of publications relating to human factors. These documents (see Figure 10.2) are very helpful in explaining the objective of human factors engineering and the importance of incorporating human factors into medical device design.

FDA has also expressed an interest in applying human factors principles to the labeling of drugs and biologics, as well as devices, but has done little to follow through with anything beyond a nod to labeling. Unfortunately, by stressing the role of human factors in product development of devices, and in focusing on labeling-related human error issues for drugs

"Human factors (HF) is the study of how people use technology. It involves the interaction of human abilities, expectations, and limitations, with work environments and system design.

The term "human factors engineering" (HFE) refers to the application of human factors principles to the design of devices and systems. It is often interchanged with the terms "human engineering," "usability engineering," or "ergonomics."

The goal of HFE is to design devices that users accept willingly and operate safely in realistic conditions. In medical applications, HFE helps improve human performance and reduce the risks associated with use error.

In many cases, HFE focuses on the device user interface (also called the UI or the man-machine interface). The user interface includes all components and accessories necessary to operate and properly maintain the device, including the controls, displays, software, logic of operation, labels, and instructions.

Specific benefits of HFE include:

- Reduced risk of device use error;
- Better understanding of device status and operation;
- Better understanding of a patient's current medical condition;
- Easier to use (or more intuitive) devices;
- Reduced need for training;
- Reduced reliance on user manuals;
- Easier to read controls and displays;
- Safer connections between devices (i.e., power cords, leads, tubes, etc.);
- More effective alarms; and
- Easier repair and maintenance.

HFE should take place early in the product development process. It should include tools such as analysis of critical tasks, use error hazard and risk analysis, and realistic use testing."

Figure 10.1 CDRH comments on human factors.
Source: CDRH, *Device Advice: Comprehensive Regulatory Assistance.*

and biologics, FDA has itself been guilty of major human factors violations in failing to take into account the following:

- Design issues are not exclusive to devices, but apply to drugs, biologics, and combination products. They all have shapes, sizes, colors, means of deployment or administration, instructions for use, susceptibility to confusion with other products, and so on.

Document Title

- *Draft Guidance for Industry and Food and Drug Administration Staff—Applying Human Factors and Usability Engineering to Optimize Medical Device Design*
- *Human Factors Implications of the New GMP Rule Overall Requirements of the New Quality System Regulation*
- *Do It by Design—An Introduction to Human Factors in Medical Devices*
- *Write It Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care*
- *Human Factors Principles for Medical Device Labeling*
- *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*
- *Human Factors Points to Consider for IDE Devices*

All of the above documents are available online from CDRH.

Figure 10.2 Examples of FDA publications on the topic of human factors.

- All medical products must in some way accommodate the characteristics of the users and of the environments in which the products are used. By definition, then, human factors come into play.
- FDA's labeling issues have been reactive to error. For example, by the time prescribing and dispensing errors were recognized because the drug trade names Celebrex (anti-inflammatory), Celexa (antidepressant), and Cerebyx (antiseizure) all look and sound similar, harm had already occurred.
- There is too much FDA focus on individual errors, as opposed to system errors. A pharmacist misreading a sloppily written prescription for Celexa and dispensing Celebrex constitutes individual error; inadequate means of generating prescriptions or of implementing patient records might be system errors contributing to that individual error. In early 2003 there was a tragic and well-publicized case in which a human heart of an incompatible tissue type was transplanted into a young girl, who later died. There were systems in place to prevent such an occurrence, yet the systems were inadequate and failed to prevent individual error.

- FDA itself has reported that of the medication errors that occurred during May 2001, 42% were attributed to human factors. Other major categories of error were communication, name confusion (see Table 10.2), labeling, and packaging/design—all of which entail human factors issues. One can only marvel at the failure of the agency to recognize this and to require human factors as essential elements in drug and biologics development, as well as in device development.
- More recent statistics confirm that medication errors are among the most common of medical errors in the United States, with *preventable* medication errors harming at least 1.5 million people every year and costing billions of dollars in excess medical expenses.[4] Confusion caused by similar drug names accounts for about 25% of medication errors.

Medical errors occur when a medical product is used incorrectly, or when there is a failure to use the product as intended. Medical products can harm patients, family members, or healthcare providers. The potential harm arises primarily from two sources:

1. Failure of the product
2. Actions of the user

Hazards associated with drugs, devices, and biologics are a serious problem. An Institute of Medicine report estimated that in the United States, between 44,000 and 98,000 people die in hospitals each year as a result of medical errors that could have been prevented. This is more than the number who die yearly from motor vehicle accidents, breast cancer, or AIDS.[3] Safer medical products can reduce the incidence and consequences of

Table 10.2 Examples of easily confused drug names.

Drug	Treatment for	Drug	Treatment for
Adderall	Attention deficit disorder	Inderal	High blood pressure
Celebrex	Pain	Celexa	Depression
Flomax	Prostate enlargement	Fosamax	Osteoporosis
Lamisil	Fungal infections	Lamictal	Epilepsy
Zantac	Ulcers	Xanax	Anxiety
Zidovudine	HIV infection	Zovirax	Herpes infections

medical errors. Attention to human factors in product design can minimize the likelihood of both product failure and product misuse.

Obviously, it also makes good business sense to take human factors seriously in the design of all new FDA-regulated healthcare products. Good products sell well; bad products can lead to lawsuits.

It is important to recognize that people interface with products on a variety of levels, including physical, perceptual or sensory, and cognitive. While no single product presentation can be ideal for all customers or users, there are areas of primary concern that can be addressed and optimized to mesh with the corporeal, psychological, and intellectual limits of the majority of customers or users.

Ergonomics is the science that deals with the dimensional and physical interfaces between humans and products. Something as fundamental as anatomical fit is surprisingly often overlooked in healthcare product development. For example, some medical devices can't be manipulated comfortably or accurately because the portions of the device required for its control are simply too large to fit in a user's hand. Average or small women, or smaller-than-average men might have this type of problem. Indeed, the majority of men or women in some ethnic groups might not be able to use such a device appropriately. The demographics of the workplace and workers must be known and accommodated to ensure that such things as size and strength of the product users are not impediments to safe and efficacious use of those products. On occasion, FDA has refused approval for a device because the clinical trials did not show that users could successfully use the device.

The individual patient, too, must be considered in human factors analyses. Small babies can not be given tablets; very elderly patients or disabled individuals may have extreme difficulty using pharmaceuticals in certain forms of administration or packaging. Devices that must conform to some part of a patient's body clearly need this type of assessment. Electrodes, cuffs, dressings, intravenous catheters, urinary catheters, flexible endoscopes, and surgical implants are obvious examples of devices that require differing sizes and conformations depending on whether they are used in neonatal, pediatric, or adult patients. Similarly, any product that is expected to be used directly by a patient must be suitable for such things as the strength, gender, dexterity, handedness, educational level, physical maturity, and functional capability of the patient.

Cognitive factors come into play in the intellectual relationship between humans and products. Is the method of handling and operation intuitive? If not, is it sufficiently easy to determine or learn how to use the product? Is the labeling informative and legible? With healthcare products,

there can be no tolerance for ambiguity. The end user—whether physician, nurse, patient, or other—must understand how, when, why, where, and how often a drug, biologic, or device is to be used.

Sometimes, cognitive elements are forgotten in the search for cosmetic appeal. Consider the gray-on-black finish and labeling on some electronic equipment such as VCRs and compact disc players. These components are very attractive, but require something just short of floodlights, five minutes, and a six-inch focal point to find the right push buttons. It's one thing to mistakenly press *rewind* rather than *play* on a tape deck. It's quite another thing to mistakenly press the wrong button on a diagnostic device because the requirements for lighting are in excess of the lighting normally available in use conditions.

This is not to say that appearances can be ignored. People do interact with products on a sensory or perceptual level too. The style, shape, or color of a product can elicit an emotional response. If that response is negative, a negative attitude is likely to be transferred to the product whether or not that product is safe, effective, and meets a market need. Healthcare products, especially, need to be presented in a manner that suggests quality and care. Product appearance and presentation and the reaction to appearance and presentation can have a significant effect on the purchaser (or influencer) and user.

As has already been emphasized, cGMP requirements for medical devices call for manufacturers to ensure that a device will perform to meet both its intended use and the needs of the user. Applying human factors principles to product design will minimize the potential for use error and for the patient injuries that come from use error. FDA suggests conducting appropriate human factors studies, analyses, and tests from the early stages of design until the point of interface of the product with the user and the patient is fixed. There are a number of ways to obtain the human factors data that relate to FDA requirements. It is wise to examine the human factors that relate to business and market advantage requirements at the same time.

In terms of human factors analysis, the goal of those involved in product development should be to:

- Know the customer
- Listen to the customer
- Observe the customer
- Act as the customer

Customer is used loosely to include purchaser, influencer, and user.

- *Identify the customer.* Who is the purchaser or who influences purchase?
- *Identify the user.* Who will be the hands-on user of the product? Is the user the customer?
- *Identify the capabilities and limitations of the user.* What are the characteristics of the physical and mental abilities of the user?
- *Identify the subject.* Who are the patients or individuals upon whom the product is being used?
- *Identify the workplace.* What is the environment in which the product will be used, and what are the limitations of the environment (for example, space, light, temperature)?
- *Identify the utility.* What is the purpose of the product and what are the clinical, market, and user needs it fills?

Figure 10.3 Examples of general questions relative to demography and products.

The cardinal rule relating to person/product interfaces in healthcare product development is: know the users and the customers. Very basically, then, the first steps in a human factors analysis might very well include the identification exercises shown in Figure 10.3. With any given healthcare product, the relative importance of each of the questions will vary, as will the relative complexity.

Within each of these identification tasks, there will be a number of subsets of activities. For example, let's consider the issue of identifying the hands-on user and obtaining critical demographic information. Suppose that it is determined that the users fit within the general category known as *nurses.* Additional data-gathering about the user profile might well address the following:

- Are the users likely to be specialists?
- Which specialties are represented by users?
- What is the level of training, education, and experience of the users?
- What is the typical ratio of male to female users?
- What are the relevant anthropometric data for the users?
- Is the size, format, configuration, labeling, packaging, and so on, of the product compatible with the users?
- Are there cross-cultural issues?

Once the user profile is identified, it is important to define and understand what the user needs are in terms of product function and performance. Once needs are understood, user expectations are determined—that is, what the user would want in terms of the product attributes. These attributes may often include the "bells and whistles." Remember, it may not be possible to fulfill all user expectations in a product. So, it is necessary to identify the combination of product characteristics discernible to the user that represent the most important product characteristics. The goals of the product design should be a match between user expectations, technological feasibility, and cost considerations. Customer feedback on positive and negative attributes of existing products and about identified or anticipated needs that are not met by existing products is extremely important. It is important to listen carefully to what customers say, predict, gripe about, and praise in terms of your products, your competitors' products, prototypes, and product concepts. Don't fall into the trap of thinking that you know more than the customers.

One particularly effective method of obtaining information about customers, users, patients, procedures, current products, and environments is through directly observed customer behavior. While techniques such as focus groups, one-on-one interviews, and surveys have value, they rely on opinions and self-reported behavior, which may not be accurate; furthermore, they can not reflect unarticulated user needs. Direct observation, on the other hand, can provide a wealth of information that simply can not be derived from questionnaires or roundtable discussions. Direct observation of diagnostic, therapeutic, surgical, and other relevant procedures is best done by a small cross-functional group. Someone skilled in human factors analysis will see problems, solutions, and opportunities that differ from those seen by a product development scientist or a marketing specialist. Thus, in addition to data critical to the development of the envisioned new product, the observation exercises may very well lead to ideas for entirely different new product opportunities.

During development stages, *formative evaluations* should be conducted to enhance the product development in progress. Formative evaluations derive information from user interaction with devices under conditions of varying degrees of formality. One such technique especially useful early in the development process is called a *cognitive walk-through*. In a cognitive walk-through, users are guided through a structured process of using a mock-up or prototype of a product. Participants are questioned and encouraged to provide feedback on any uncertainties or difficulties they notice while using the product.

Another formative evaluation approach is *simulated use testing* (also called *usability testing* or *user testing*), which involves systematic collection

of data from participants using a product (or mock-up or prototype) in realistic situations.

Studies under simulated conditions can be used early in the design process to clarify suspected or known problems with product use, demonstrate that use-related hazards have been addressed, evaluate candidate design alternatives, and validate safe and effective use by intended users.

Formative studies that involve use of the device by representative end users are useful for identifying problems that were not identified or sufficiently understood using other analytical methods earlier in the design process. To reiterate what was said in earlier chapters of this book, it is usually easier and more cost-effective to address and resolve problems in early design stages.[5]

Beyond observation in formative evaluations, the greatest degree of empathy and identification with the customer is to actually act as the customer would act, to whatever extent possible. This entails putting oneself into the place of the customer (or user) in a real use or simulated setting. If a medical device can be manipulated and deployed without direct involvement with or compromise to a patient, those in a product development organization should make every effort to manipulate and deploy existing products and product prototypes in actual use situations. If the opportunity for this exercise is not possible in a clinical setting because of possible risk to patients, personnel, equipment, or so forth, role-playing in simulated situations is possible. Using products and prototypes in preclinical operative or therapeutic procedures, using anatomical models, and creating mock scenarios all allow one to put oneself into something approximating the role of the customer in terms of assessing human factors and product design.

If, following human factors analysis, it is determined that a new product concept or new product—in its entirety—is not fully compatible with its potential users, a business decision will have to balance the trade-offs between alternatives. Should the product be redesigned to increase its acceptability to the users? Should multiple versions or sizes be made available? Or is the risk of nonuse or misuse of the product because of its human factors limitations acceptable to the company from both a potential product liability perspective and a reduced market share perspective? Market need, of course, must be clearly identified or firmly created. The element of utility is extremely important to human factors consideration. It is clearly a waste of time, money, and energy to develop a healthcare product that can not be matched to an identified customer or market need.

One issue affecting human factors assessment is the drive toward design and development of a new healthcare product for worldwide markets. The globalization trend in product development is likely to be met

with unanticipated product launch flops if human factors are not carefully considered. In addition to the more obvious factors such as size differences among some populations, there are cognitive factors that can have significant impact on the acceptability of a product. Background, education, and training of the product users in some third world countries, for example, may differ substantially from that of users in the United States. These differences, in turn, may necessitate major design or labeling modifications to assure use of a product at all, much less safe and effective use of the product.

Cultural biases involving diagnostic and therapeutic procedures can work against a successful global development and launch of a new product, as can differences in attitudes toward the significance of particular symptoms. There has been a history of preference for certain types of procedures and therapies, as well as a reluctance to engage in other practices associated with particular countries. These opinions will affect the perceived clinical utility of a given healthcare product. It is important not to overlook these culturally related human factors if a new product is to be introduced into markets in different cultures or into multicultural markets.

Applying human factors principles to product development will allow an integration of user/customer requirements, user/customer expectations, clinical utility, marketing needs, and cost considerations into product design. Product development requires designing a relationship between technology and people.

11

Is It Safe and Does It Work?

Evaluating Safety and Efficacy in Clinical Trials

Test everything. Keep what is good.

—I Thessalonians 5:21

Before a medical product can be marketed in the United States, FDA must be given reasonable confidence that the product will be safe and effective when it is used. For most new drugs, biologics, Class III devices, and some Class II devices, reasonable confidence comes by way of clinical trials—that is, studies in humans. Clinical trial failures claim a great financial toll on the medical products industry. Failures occur when a company terminates a study because the product is not effective, or worse, causes unexpected harm, or when the completed trials fail to satisfy FDA requirements for adequate and rigorous demonstration of safety and efficacy. It is never possible to guarantee the results of a clinical trial, or there would be no need for such trials in the first place. So, planning, design, and execution are especially important. For example, critical determinations include the selection of the control treatment, how to measure the clinical endpoints, the number of patients required to demonstrate safety and to provide the statistical basis for efficacy, and the choice of whether a trial will be based on non-inferiority (that is, no worse than the control) or superiority (significantly better than the control).

Before a drug, biologic, or device can be tested in humans, though, there must be compelling evidence that the product is safe enough to test in people. To establish that a medical product is reasonably safe, new products being developed are subjected to a variety of laboratory and animal tests.

PRECLINICAL TESTING

Preclinical (or *nonclinical*) *testing* refers to evaluations of both safety and efficacy in *in vitro*, *ex vivo*, or *in vivo* systems other than in human beings. It is estimated that only five in every 5000 to 10,000 pharmaceuticals that enter preclinical testing advance to human trials, and that of these five, only one will eventually be marketed as a new product.[1]

Although the principal purpose of preclinical testing is to provide evidence of safety and performance before involving human subjects, in some instances the testing may suffice in lieu of testing in humans. For example, some medical products for which it would be unethical or not feasible to conduct clinical trials may be approved by FDA based on animal studies.[2]

Odds of successfully progressing through preclinical testing are generally better for medical devices. By definition, devices do not involve metabolic processes for their primary effect. In contrast to the drug development process, development of medical devices does not usually involve screening enormous numbers of candidate technologies. Furthermore, it is usually easier to design safety and efficacy into a device using principles of mechanics and human factors than it is to design safety and efficacy into a pharmaceutical through molecular modeling. All of this means that many device types can be extensively and accurately evaluated in mechanical or anatomical models and in chemical, biological, and physical laboratory test procedures. Simulated-use testing of prototype designs can quickly weed out devices not likely to succeed before animals need to be involved. Implantable and absorbable medical devices, however, are somewhat more similar to drugs in their testing requirements since properties such as long-term effects, metabolic fate, excretion, and storage profiles often must be examined. Nevertheless, the chemical and biological evaluations of pharmaceuticals and devices involve differing experimental approaches.

FDA has guidelines and regulations regarding the type of data and results it expects to see for pharmaceuticals before considering testing on humans, but the agency generally does not tell drug companies what specific laboratory evaluations or animal tests to run. It is important, however, to ensure the quality and reliability of preclinical safety studies. This is normally accomplished through the conduct of the safety studies in compliance with *good laboratory practice* (GLP) regulations, which emphasize quality and ethics. To this end, the agency offers guidelines dealing with GLPs, which outline the requirements for quality assurance.[3] GLPs essentially impose the use of quality standards covering a number of elements of preclinical testing, particularly:

- Organization and personnel
- Facilities
- Equipment
- Testing facilities operation
- Test materials and control materials
- Protocols
- Record keeping and reports

In vivo or in vitro nonclinical laboratory studies to provide safety data in support of marketing applications for drugs, biologics, and medical devices must be done according to GLP unless there is a compelling and justifiable reason to be tested outside of GLP requirements. Certain other studies—for example, screening, dose ranging, and preliminary efficacy studies—are exempt from GLP requirements. One caveat for product developers is that the universities with whom many contract for conduct of preclinical studies frequently do not comply with GLP requirements. Laboratory choice is critically important.

The nature of the drug (and of many biologics) being tested and the clinical test plans give scope and definition to the specific preclinical protocols and studies that are required to demonstrate safety and efficacy. Occasionally, customary animal models may be inappropriate or unsuited to a new product being tested. In this case, the test sponsors are encouraged to discuss testing approaches with FDA.

Biological evaluations of medical devices to determine the potential toxicity resulting from contact of the device materials with the body are typically more defined than they are for drugs or biologics. Testing is designed to determine that the device materials (1) do not produce adverse local or systemic effects, (2) are not carcinogenic, and (3) do not cause adverse reproductive or developmental effects. In 1995, FDA agreed to replace its existing guidance on biocompatibility with ISO 10993 *Biological evaluation of medical devices—Part 1* with some modifications added to areas where FDA did not regard the international guidance as having adequate rigor.[4] Tables 11.1 and 11.2 show the harmonized test matrices.

The overall problem with preclinical trials is that they are not all that effective in predicting the safety and effectiveness of a drug, biologic, or medical device in humans. Remember that before a product can be advanced to clinical trials, it must have successfully negotiated the "valley of death" of preclinical testing. Yet the majority of products that do make

Table 11.1 Initial evaluation tests for consideration: biological evaluation of medical devices.

Medical device categorization by			**Biological effect**							
Nature of body contact (see 4.2)		**Contact duration** (see 4.3) **A—limited** (< 24h) **B—prolonged** (24 h to 30 days) **C—permanent** (> 30 days)	**Cytotoxicity**	**Sensitization**	**Irritation or intracutaneous reactivity**	**Systemic toxicity (acute)**	**Subacute and subchronic toxicity**	**Genotoxicity**	**Implantation**	**Haemocompatibility**
Category	**Contact**									
Surface device	Skin	A	x	x	x					
		B	x	x	x					
		C	x	x	x					
	Mucosal membrane	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
	Breached or compromised surface	A	x	x	x					
		B	x	x	x					
		C	x	x	x		x	x		
External communicating device	Blood path, indirect	A	x	x	x	x				x
		B	x	x	x	x				x
		C	x	x		x	x	x		x
	Tissue/bone/ dentin	A	x	x	x					
		B	x	x	x	x	x	x	x	
		C	x	x	x	x	x	x	x	
	Circulating blood	A	x	x	x	x				x
		B	x	x	x	x		x		x
		C	x	x	x	x	x	x		x
Implant device	Tissue/bone	A	x	x	x					
		B	x	x	x	x	x	x	x	
		C	x	x	x	x	x	x	x	
	Blood	A	x	x	x	x	x		x	x
		B	x	x	x	x	x	x	x	x
		C	x	x	x	x	x	x	x	x

Source: ISO 10993-1:2003(E).

Table 11.2 Supplementary evaluation tests for consideration: biological evaluation of medical devices.

Medical device categorization by			**Biological effect**			
Nature of body contact (see 4.2)		**Contact duration** (see 4.3) **A—limited** (< 24h) **B—prolonged** (24 h to 30 days) **C—permanent** (> 30 days)	**Chronic toxicity**	**Carcinogenicity**	**Reproductive/developmental**	**Biodegradation**
Category	**Contact**					
Surface device	Skin	A				
		B				
		C				
	Mucosal membrane	A				
		B				
		C				
	Breached or compromised surface	A				
		B				
		C				
External communicating device	Blood path, indirect	A				
		B				
		C	x	x		
	Tissue/bone/ dentin	A				
		B				
		C	x	x		
	Circulating blood	A				
		B				
		C	x	x		
Implant device	Tissue/bone	A				
		B				
		C	x	x		
	Blood	A				
		B				
		C	x	x		

Source: ISO 10993-1:2003(E).

it into clinical trials will fail anyway, never making it to market, which clearly indicates the inadequacy of preclinical programs. Too often, even if a product advances to clinical trials, the trials will either be discontinued or, if completed, the product will fail to gain FDA approval because of trial design or execution inadequacies.

CLINICAL TRIALS

When sufficient preclinical data establishing that the product is reasonably safe for testing in humans, and that there is reason to suggest that the product has clinical efficacy, a petition may be filed with FDA to obtain permission to evaluate the as yet unapproved (or uncleared) drug, biologic, or device in studies involving humans. Tests of this nature in human participants are known as *clinical trials.* For drugs and biologics, the application for permission to conduct clinical trials is known as an Investigational New Drug (IND) application, while for medical devices, a request for an Investigational Device Exemption (IDE) is made. The format and content of INDs and IDEs have been discussed earlier in this book.

Although clinical trials have been conducted for decades within the context of quality systems known as *good clinical practices* (GCPs), international efforts to harmonize good clinical trial design are relatively recent. In 1997, FDA published guidelines on GCP under the auspices of the International Conference on Harmonization (ICH).[5] The document defines GCP as an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. This standard has its origin in the Declaration of Helsinki, a document dating back to 1964 and revised since, which embodies ethical and scientific principles for studies involving human subjects. The ICH guidance for GCP is intended to provide a unified standard to facilitate mutual acceptance of clinical data in the United States, the European Union, and Japan. Thirteen basic principles are described in the document, which stresses that quality assurance must be built into all aspects of a clinical study (see Figure 11.1). Both CDER and CBER were among the ICH sponsors of the guideline, which is directed to pharmaceutical studies. Nonetheless, the guideline is highly relevant to medical device clinical trials as well, and, with time, the substance of the document is likely to hold considerable influence with CDRH and with the medical device review activities of international regulatory agencies.

FDA regulations require all research plans involving human testing of FDA-regulated medical products to be reviewed and approved by an

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol and amendment(s) that have received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favorable opinion.
7. The medical care given to, and medical decisions made for, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol and amendment(s).
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Figure 11.1 Principles of ICH GCP.

institutional review board (IRB) before clinical testing can begin. These review boards exist in hospitals, academic centers, and research institutions at which clinical trials take place. An IRB also conducts at least an annual review throughout the duration of an approved clinical trial. The purpose of the IRB review is to ensure that risks to subjects are minimized, informed consent is obtained and documented for each subject, selection of subjects is fair and equitable, risks to subjects are reasonable in relation to expected benefit, and that privacy and confidentiality of subjects are protected. At least five people with varying backgrounds make up an IRB. They are usually knowledgeable in the relevant research areas, but at least one member must be in a nonscientific discipline, and at least one member must not be affiliated with the institution. An IRB may refuse to allow a clinical trial to be conducted at its institution if it perceives the study as not safe enough or as not providing any therapeutic benefit to the patient.

DRUGS AND BIOLOGICS

Clinical trials of drugs and biologic pharmaceuticals typically consist of three preapproval phases, and one or more post-approval phases.

Phase I (sometimes Arabic numerals are used, rather than Roman numerals), involving a relatively small number of healthy volunteers, is geared toward determining side effects and gathering initial safety information. If everything goes appropriately in phase I, the test material may go on to the next phase.

Phase II trials involve a larger number of subjects who have the condition the product is intended to treat. Phase II trials are often—indeed ideally—double-blinded (neither the investigator nor the patient knows whether the investigational treatment or a control is used), randomized, controlled trials and are designed to determine optimal dosage levels and to detect short-term side effects, as well as to gain a preliminary indication of effectiveness. If a test product makes it through phase II, it usually is moved into phase III.

Phase III trials involve large numbers of subjects—often thousands—usually in double-blinded, randomized, controlled studies conducted at multiple test sites. In phase III, detailed data are gathered about the effectiveness of the pharmaceutical in comparison to control treatments. Subjects are followed to evaluate long-term side effects and safety.

Phase IV trials are done after the product has been marketed. These studies are designed to further monitor effectiveness of the approved intervention in the general population and to collect information about any safety issues and adverse effects associated with widespread use.

ENDPOINTS AND BIOMARKERS

Here is an extremely important point for consideration in product development planning: choose clinical endpoints carefully, with focus on appropriate, convincing measures of the clinical effect that you wish to evaluate. The difference in efficacy for your test product, compared to the control treatment, may be *statistically* significant, but not *clinically* significant. The endpoint must accurately represent a clinical characteristic that is worthy of medical intervention.

At the conclusion of the clinical trials (assuming all has gone well), an NDA is submitted to FDA requesting approval to market a new drug. In the case of a biologic, the submission for marketing approval is a BLA. Figure 11.2 provides an overview of the new drug development and approval process. As can be seen, clinical trial failure rates are high. The reasons for failure are:

In phase II

- 51% insufficient efficacy
- 29% strategic reasons

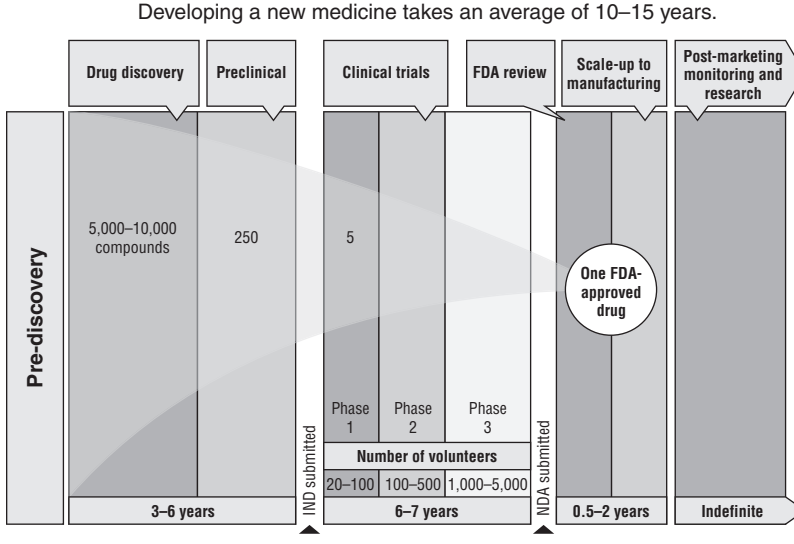

Figure 11.2 Drug development pathway.

Source: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development: Understanding the R&D Process, www.Innovation.org.

- 19% safety concerns[6]

In phase III

- 66% lack of efficacy
- 21% safety concerns
- 7% financial and/or commercial reasons[7]

The *Common Technical Document* (CTD) is one component of ICH efforts with regard to the harmonization of requirements for the approval of pharmaceuticals. FDA has exerted considerable effort in the development of the ICH drug application document known as the CTD.[8] The CTD is a prescribed organization of the information required to be submitted to a regulatory authority; it does not define the requirements, quality, or quantity of content of an application. Indeed, there are many regional requirements, as well as applicants' preferences, that affect the contents of a CTD submitted in each ICH region. Thus, according to FDA, the BLA and the NDA will not disappear with the adoption of the CTD format. Unlike the European Union and Japan, the United States does not plan to make use of the CTD mandatory. The agency does, however, hope that use of the CTD format will help to standardize the presentation of information in drug and biologics applications, and thus make review a bit easier. The harmonized document comprises five modules, as shown in Figure 11.3.

MEDICAL DEVICES

Although conducting clinical trials has a long-established history when it comes to drugs, the situation is quite different when it comes to medical devices. In the mid-1990s, only approximately 10% of all medical device submissions to CDRH included clinical data as part of the scientific evidence in support of product claims. FDA has taken steps toward imposing more stringent requirements for device clinical trials, especially those trials used in support of Class III devices requiring PMAs.[9] Federal law requires that the safety and effectiveness of a device are to be determined:

- With respect to the persons for whose use the device is represented or intended
- With respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and
- Weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use

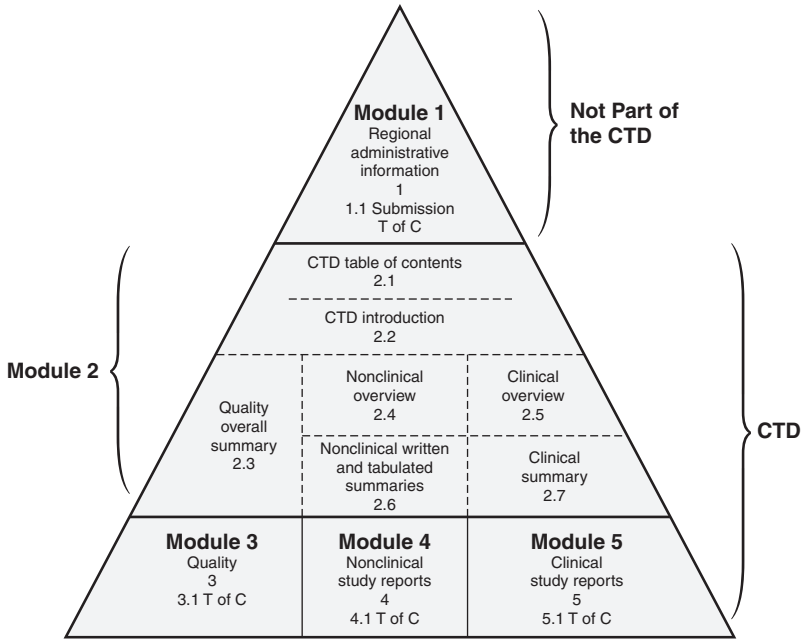

Figure 11.3 Diagrammatic representation of the ICH Common Technical Document.

There are significant differences in the logistics of conducting clinical trials on medical devices. Blinding is often not possible in device studies. For example, it might be impossible to arrange for a surgeon not to be able to ascertain whether she or he is using an investigational device or not since a pill-type placebo or sham version of a three-dimensional, functional mechanical item—especially if it is used to perform a therapeutic action or if it is an implantable device—simply may not be possible to create and use safely or ethically. Choosing appropriate controls for controlled medical device studies is also more problematic than selecting controls for drug or biologics clinical studies. In drug studies, controls usually consist of a placebo, which has no biological activity, or another drug that has already been approved for the condition being treated. The subject can, for example, take a pill or get a shot, and neither the subject nor the investigator will know whether what has been administered is the test agent or control. But controls for medical device trials may typically be an acceptable standard of care. Standards of care can be older versions of the same device, different devices that have been approved or cleared, devices that look the same

as the test device but do not deliver therapy (shams), non-device therapies, or no therapy at all—all of which are commonly discernable to the investigator. Here are some other unique aspects of medical device clinical trials:

- Compared to drug studies, medical device trials tend to involve relatively few subjects, although each subject might require a longer follow-up.
- Use of a device is often just part of a complex therapeutic procedure.
- The success of the procedure frequently depends on factors other than the device, such as the skill of a surgeon or the extent of a surgical intervention.
- Clinical trials of some in vitro diagnostic devices may not require an IDE at all, provided that the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established product or procedure.
- There are different requirements for what FDA considers significant-risk devices and nonsignificant-risk devices.

Traditional phase I studies on medical devices are often not possible. Devices that are used invasively, for example, or that deliver radiation, would be inappropriate for use in safety evaluations on healthy volunteers. There is a greater tendency to view device trials as being either small-scale *feasibility* or *pilot* studies or as being the larger-scope *pivotal studies.*

In order to resolve issues such as device design, device operation, and patient population, FDA encourages medical device companies to conduct small-scale pilot or feasibility studies prior to initiating a pivotal clinical trial—a *pivotal trial* being one that will yield the clinical data used to support a submission for approval or clearance. A pilot study usually involves fewer than 20 patients while a pivotal device trial may involve several hundred patients and often is conducted at multiple sites.

Evidence from one or more well-controlled pivotal clinical studies generally serves as the primary basis for the determination of reasonable assurance of safety and effectiveness of the medical device required by a Premarket Approval (PMA) application. However, the regulations provide FDA with some flexibility regarding its determination of the type of evidence, including preclinical data, that may be considered valid scientific evidence to demonstrate the safety of a medical device. Clinical studies

are also increasingly required in support of certain Class II medical device 510(k) submissions.

After a successful clinical trial, a PMA application for marketing approval or a 510(k) application for marketing clearance (if FDA has determined that clinical testing is required) is filed with FDA, depending on the device class and requirements.

As with drugs and biologics in phase IV studies, when a medical device has been approved or cleared for marketing by FDA, it is not uncommon to conduct focused, limited clinical *post-marketing* studies. These studies are generally conducted to comply with FDA requirements for continued monitoring or to support marketing efforts by generating additional performance, safety, or economic data.

Many medical products companies engage the services of a *contract research organization* (CRO) to assist in the planning, execution, and follow-up of clinical trials. CROs provide a wide variety of services, such as protocol development, data management and analysis, and preparation of FDA submission documents. It is virtually impossible for a small company to independently conduct a clinical trial, and even large companies often use CROs for selected tasks.

DIVERSITY IN CLINICAL TRIALS

Variations in response to medical products and procedures have been observed among distinct groups within the population of the United States. Age, gender, size, and ethnic origin can independently or collectively influence the effects of medical and surgical treatments. With some procedures, these factors do not seem to matter or need to be taken into account at all. The same volume dose of influenza vaccine is used whether an adult patient weighs 95 pounds or 295 pounds, whether male or female; but weight and gender have considerable implications for the use of anesthesia in surgery.

The reasons for the diverse responses to medical treatments are manifold, and appear to include both known and probable intrinsic and extrinsic factors, or a combination of the two. *Intrinsic factors* primarily reflect the effect of genetic or physiologic differences, while *extrinsic factors* are tied to environment. Pharmacogenetic research has uncovered significant differences associated with race or ethnicity in the metabolism, clinical effectiveness, and side-effect profiles of many drugs.

Unfortunately, the medical products industry has had some difficulty in getting its arms around this issue. Unless a product is specifically designed for use within a population subgroup, the subjects of clinical trials

for drugs, biologics, and medical devices have tended to be rather homogeneous. Historically, women and children have been neglected in clinical trials, and ethnicity of patients has been rarely recorded, much less evaluated for association with treatment response. Consequently, the specific treatment requirements and responses of the very young, the very old, women, and minority Americans—especially those of African, Asian, and Hispanic heritage—have been ignored. Partly for this reason, substantial disparities exist in the quality and quantity of medical care received by these population subsets. FDA has recently begun to address ethnic diversity in clinical trials by providing industry with opinions and guidances.[10]

By encouraging diversity as a factor to be included at all stages of development of a medical product, FDA hopes that industry and FDA will be better positioned to understand how medical products will affect different populations when they reach the market. Information that is gathered during development and clinical evaluations can then be used to refine product labeling, patient selection, and dose selection. The desired outcome is the marketing of safer and more effective medical products.

FDA is working to improve the science behind certain clinical trial designs. Recent advances in two clinical trial designs—*non-inferiority* and *adaptive* designs—have required FDA to conduct more-complex reviews of clinical trial protocols and new marketing applications. Non-inferiority studies are intended to show that the difference between the new and active control treatment is small enough to allow the known effectiveness of the active control to support the conclusion that the new test treatment is also effective.[11] Adaptive trial designs allow the use of interim clinical data to modify and improve the study design in a preplanned manner.[12] There are formidable challenges in the design, statistical analysis, and interpretation of these clinical approaches. Improving the scientific bases of these trial designs should, however, add efficiency to the drug review process, encourage the development of novel products, and speed new therapies to patients.

12

How Much Is the Product Really Worth?

Outcomes Research, Pharmacoeconomics, and Managed Care

Not everything that can be counted counts, and not everything that counts can be counted.

—Albert Einstein

Efficacy refers to the findings in an adequate and well-controlled clinical trial. *Effectiveness* refers to the clinical effects in real-life use situations. There is pronounced interest in how the vast healthcare expenditures in the United States are being directed, and whether there is really value in terms of effects on health and on society as a result of these expenditures. In an environment of both escalating healthcare expenditures and limited funding resources, cost containment has become a major concern for patients, healthcare providers, and insurance payers. Therefore, it is becoming more and more important for clinical trials of all types of healthcare products to be designed to address outcomes other than simply functional clinical efficacy and safety. Outcomes research comprises studies that are conducted in order to measure the end result of medical treatment and the effect of that treatment on the health and well-being of patients.

Today, there is a higher demand for products that demonstrate they will also provide positive outcomes in terms of clinical utility, cost-effectiveness, and quality of life. The need is obvious if one considers that it has been estimated that only 10–20% of all medical procedures performed in the United States have ever been proved either efficacious or effective in randomized controlled clinical trials.[1]

In comparison to clinical research, which evaluates the safety and efficacy of medical technology, outcomes research examines whether the technology increases survival, reduces morbidity, improves any number of

aspects of quality of life, and provides benefits that justify the costs of its use. Ideally, risk/benefit ratios should take priority over cost concerns. Costs, in turn, should include cost-effectiveness analyses that assess not only the immediate outcome and associated costs, but also the long-term effects and results of treatment and the impact on future costs and societal benefits. Two powerful forces are driving the trend to conduct outcomes research: (1) reforms to healthcare provider systems, especially that phenomenon known as *managed care,* and (2) the astounding rate of technological, biotechnological, and procedural advances, which increase the number of available options in the practice of healthcare.

Managed care refers to healthcare, provided by a prepaid health plan or covered by an insurance program, in which medical services for covered patients are reviewed and coordinated with the intent of managing access to care, quality of care, and cost of care. The overriding concern for cost containment is approached through a variety of ways, such as closed formularies (restricting the therapeutic agents that will be covered or reimbursed), requiring the use of generic drugs whenever they are available, using primary care physicians as "gatekeepers" to make decisions about treatment or referral to specialists, and relying on outcomes research to provide standards for acceptance and coverage of medical treatments, including the use of drugs, biologics, and medical devices. Many of us might argue that managed care is actually a contraction of, "you're lucky if you *managed* to get any *care* at all."

As yet, there are no national, much less international, standards for outcomes evaluations. Although there is sloppiness in the consistency of terminology and in consensus of opinion, outcomes research has primarily concentrated on various types of economic analyses and on quality-of-life measurements. Economic analyses of healthcare products attempt to answer questions about the use of the products, such as:

- What are the direct and indirect costs of the intervention?
- What are the costs compared to those associated with the use of other products?
- What are the cost savings related to reduced need for medical follow-up or for additional treatment?
- What are the cost advantages of avoiding hospitalization?
- What is the economic impact of earlier return of the patient to the workforce?
- What is the economic impact of lives saved?

- What are the costs associated with early diagnosis?
- What is the economic impact of disease prevention?

CLINICAL OUTCOMES

Clinical outcomes are the results of a medical intervention in planned and, to some degree, controlled studies. The basic assumption is that the clinical differences observed between a treatment group and a control group are due to the treatment. The evaluation of clinical safety and efficacy through the clinical trials process is discussed in a separate chapter. In real life, as opposed to controlled clinical trials, many uncontrollable and even unidentifiable factors affect the clinical benefits of a medical product. The physical environment and location, experience of practitioners, health status of the patient, and concomitant medical treatment of the patient are a few of the variables that can hinder or help the clinical outcomes derived from a medical product. Information on product real-life effectiveness is generated through post-marketing surveillance and reports.

PHARMACOECONOMICS AND ECONOMIC OUTCOMES

A basic definition of *pharmacoeconomics* is: the application of economic principles to the evaluation of pharmaceutical therapy interventions. Through a comparison of costs and consequences of the use of various pharmaceutical products and services, the objective of pharmacoeconomic analysis is to improve public health through improved, rational decision making. The major analytical methods used in pharmacoeconomic analyses are cost-effectiveness analysis (CEA), cost-minimization analysis (CMA), cost/utility analysis (CUA), and cost/benefit analysis (CBA).[2] Recently, there has been growing interest in applying the principles of pharmacoeconomics to evaluate the economics of use of all medical products, and to medical and surgical procedures as well. Examples of economic analysis techniques are shown in Table 12.1.

QUALITY-OF-LIFE OUTCOMES

Quality of life (QOL) assessments comprise evaluations of patient-oriented factors. The relevant domains are related to the status of the patient's physical and mental health, functional status, and general health perceptions (see

Table 12.1 Common pharmacoeconomic methods.

Method	Objective
Cost-effectiveness analysis (CEA)	Compare costs and consequences of two alternative treatments, with costs measured in monetary terms and effectiveness measured in outcome units. A cost-effective treatment may not be less expensive if it provides additional benefit that is worth the extra cost.
Cost-minimization analysis (CMA)	Determine the least expensive alternative among products with equivalent safety and efficacy. This is the simplest method of analysis.
Cost/utility analysis (CUA)	Compare costs and consequences of a treatment, with costs measured in monetary units and consequences measured in terms of patient preferences of one outcome over another (often expressed in terms of QOL)
Cost/benefit analysis (CBA)	Measure costs and benefits, all of which are expressed in monetary units. CBA requires the conversion of disparate outcomes into standard monetary units, and can be used to determine which choice has the greater potential to benefit society, based on resource allotment.

Table 12.2 Examples of quality-of-life domains.

Domain	Attributes
Physical health	Symptoms, pain
Mental health	Well-being, life satisfaction, anxiety, depression, cognitive functioning
Social functioning	Personal and community interactions
Role functioning	Work, task, and household management
General health perceptions	Satisfaction with healthcare, energy

Table 12.2). Although life-quality factors are extremely important, they are difficult to measure quantitatively. QOL depends on an individual's perceptions, beliefs, feelings, and expectations. The person's own appraisal of his or her health and well-being is a key factor in QOL studies. Questionnaires and interviews are common tools to evaluate QOL outcomes, and results are thus subject to collection and interpretation being influenced by

culture, gender, age, and honesty. Furthermore, the individual appraisals must be consistent and reproducible enough to be extrapolated to an entire patient population.

COMPARATIVE EFFECTIVENESS RESEARCH

Interest in *comparative effectiveness research* (CER), also known as *patient-centered outcomes research* (PCOR), could have a major future impact on medical product development. Translational research is regarded as an important contributing element in data generation and sharing relevant to CER.

In a 2009 Report to Congress, comparative effectiveness research is defined as:

> . . . the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances.[3]

The report points out the following:

- To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and subgroups.
- Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies.
- This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.

Some questions that could be addressed by CER are shown in Figure 12.1. The methodology of CER evaluations is not fully worked out yet, and FDA has no requirement for CER in its review and approval processes. But with increased private sector pressures for cost containment and increased

- Does it work better than alternatives in some or all patients?
- Does it work faster than alternatives in some or all patients?
- Can it be added to other treatments?
- Is there any additional benefit in some or all patients?
- Is it effective under conditions when alternatives fail?
- Is it comparably safe and effective, but cheaper or more readily available?

Figure 12.1 Questions applicable to CER.

government role in payment for healthcare, we should prepare for scientific, legal, economic, political, and regulatory participation in CER.

OUTCOMES AND PRODUCT DEVELOPMENT PLANNING

When planning for or developing a new product, it is important for the entire organization to understand the purpose of the product, and to consider the marketing wish list for that product. In early stages of development, desired outcomes are highly relevant to product design. Remember, form follows function (well, usually). Planning for appropriate preclinical evaluations and developing the treatment models for preclinical efficacy studies should be geared toward all clinical outcomes of interest. Finally, the clinical trials themselves must be designed to encompass endpoints that will demonstrate, if successful, the desired outcomes.

In the selection of outcomes, the product development planning team must ask and answer the following questions:

- What would we like to know?
- What would we like to show?
- Is it likely to be worth the development to know or show?
- Is there a great likelihood that the product will provide either (1) a benefit that will justify higher cost, or (2) comparable benefits to existing therapies at a lower cost?

Regardless of the category, any outcomes measure should ideally be:

- Directly associated with a benefit to the patient

- Relevant to the medical treatment
- Unambiguous and definable
- Mutually exclusive to alternative outcomes
- Quantifiable
- Reproducible in repeated treatments
- Statistically significant

Outcomes evaluations of one sort or another have been misused by some medical products manufacturers in order to create a marketing edge. It has been far too routine to see or hear advertisements for products that claimed to be better, safer, and more cost-effective than competitive products. QOL outcomes are implied by words and pictures of people feeling more energetic, smarter, and happier as a result of using a product. This is an ethical and legal issue if the claims are unsubstantiated and misleading. FDA currently expects outcomes claims to be based on well-controlled clinical trials. Well-established guidelines will help to eliminate the skepticism that can arise when a company has a vested interest in the pharmacoeconomic analysis of its own product. Nevertheless, the enormous investments in medical product development, coupled with risks in marketability, constitute a powerful incentive for manufacturers to obtain economic data to support new products.

Meanwhile, healthcare reform and evolving controversies over resource allocations, drug pricing, and reimbursement will demand more rigorous data to justify expenditures based on clinical and humanistic outcomes as well as cost. While FDA, as yet, has no formal defined policy or requirement for outcomes research and purports to have no concern about product costs when reviewing submissions, the agency has expressed strong interest in seeing data demonstrating clinical utility, comparative efficacy, and QOL outcomes. We can expect to see interest in outcomes research continue to increase, and should be ever aware that outcomes issues need to be included in product development planning.

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Part III

Product Development Planning

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13

Models and Metaphors

Product Development and the Product Development Organization

Every idea has something of the pain and peril of childbirth about it.

—Samuel Butler

The concept of product development is often schematically presented as a horizontal or vertical funnel (see Figure 13.1). This structure illustrates the principle that a successful development strategy begins with a multitude of new product ideas. These ideas are represented by numerous inclusions at the wide end of the funnel. Each of the ideas can be thought of as a potential project, and thus as a possible future product. Since there are always more potential projects than there are financial or human resources to allot to them, the ideas are subjected to some type of scrutiny, selectively eliminating those that are less desirable or feasible while retaining those most worthy of pursuit. Eventually, the idea pool is narrowed enough that a significant investment can be made to bring a few of the most promising projects through development and on to product launch. Launched new products are depicted as blebs exiting the narrow end of the funnel.[1,2]

Depending on the nature of a given business, the project-focusing process may require hundreds of possibilities entering the open end of the funnel in order to yield just one commercializable product from the narrow end of the funnel. This is especially true in the pharmaceutical industry, where molecular modeling and trial-and-error screening can involve the consideration of a vast number of drug candidates. In any given segment of the medical device industry the numbers are likely to be quite different, with perhaps 10–100 ideas potentially available to enter the funnel.

In the development of FDA-regulated healthcare products, the number of new products emerging from the funnel depends on a variety of internal and external factors. Technical feasibility is one. An idea may be incredibly

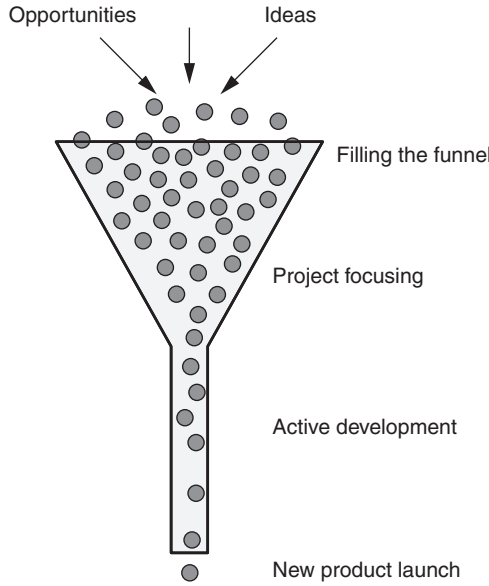

Figure 13.1 Stylized new product development funnel.

interesting but not realistically achievable within a century—which may be longer than the company cares to wait. Similarly, a market opportunity for an idea may or may not exist now or be likely to exist when the idea could become an actual new product. There are numerous issues and hurdles that must be identified and assessed.

Models of this sort often make things look too easy. Product development appears too automatic a process. The models seem to suggest that the hardest part of product development is choosing from among the dozens, scores, or hundreds of opportunities waiting in the wings. The models, in other words, seem to suggest a guaranteed outcome of commercialized products as long as one does a good job of drawing a funnel.

SWIMMING AGAINST THE STREAM

The development of new FDA-regulated healthcare products is an uphill struggle with no guarantees. A more appropriate metaphor for a model would be that of salmon swimming upstream, against incredible odds, to spawn and ensure the continuance of the species. Salmon swim upstream, from ocean to freshwater, for distances of up to 2000 miles on a journey

that may take months. In their fight against rushing currents, 10-foot waterfalls, and treacherous rapids, there are significant casualties. Weak fish become exhausted and are washed away with the flow of the rushing water. Others are dashed against rocks or fail to clear obstacles in the stream, becoming stranded and doomed to die. Bears lurk on the banks, knocking the fish out of the water and greedily devouring them. Then there are the sport and commercial fishermen waiting for their take. It's not an easy trip.

Let's consider how this natural adventure relates to healthcare product development, with the trip upstream signifying the development pathway, and spawning signifying the launch of new products. This allows the business (the species) to go on. The masses of oceanic salmon on their way to spawn represent the large idea and opportunity pool, and the current coursing against them represents changing, evolving elements that impede progress. Large rocks and rapids are factors in the internal and external environment that we recognize and over which we may even have some degree of control. Finally, the grizzly bears and fishermen stand for conditions in the internal and external environment over which we (that is, the product developers) have no control. Examples of various types of impediments are given in Figures 13.2 to 13.5.

In this model, the role of a defined product development process with documented design controls is to minimize the negative impact of certain obstacles by serving in part (to be consistent with the model) as a fish ladder. Fish ladders are artificial sloping waterfalls that are built to help the salmon travel over dams and other virtually nonnegotiable areas. The ladder of process will increase the likelihood of survival of the fittest projects and maximize the opportunity of those projects to be transformed into successful, profitable new products. Additionally, a sound product development process will provide navigational maps identifying the location and magnitude of hazards and will help provide the knowledge and facility necessary to avoid or overcome obstacles.

While evocative of the challenges, obstacles, and hazards confronting healthcare product development, this model is somewhat extravagant and certainly unconventional. For the sake of simplicity, then, reference to funnel models will be the norm in later discussions of the product development process.

THE CROSS-FUNCTIONAL ORGANIZATION

What, then, does it take for a healthcare company to guide and propel new product opportunities through the treacherous and labyrinthine course that

Rocks—navigate by knowledge and planning

- Costs
- Design creep
- Reluctance to kill hopeless projects
- Lack of processes
- Enslavement by processes
- Design flaws
- Insufficient intellectual property protection
- Too many meetings
- Too few meetings
- Poorly trained teams
- Not planning for future technologies
- Insufficient knowledge of regulatory issues
- No formal product development planning
- Team conflict
- Too many projects
- Wrong skill sets
- Wrong mix of projects
- Unclear product concept
- Not prioritizing projects
- Lack of formal reviews
- Lack of focus on quality

Figure 13.2 Internal impediments to medical product development that can be controlled or influenced by a product development organization (salmon swimming upstream analogy).

lies ahead? It takes a talented, committed multidisciplinary product development organization, with each member qualified for his or her responsibilities through education, training, and experience (see Figure 13.6). The first paradigm shift that has to take place is to not equate or confuse "product development," especially in the context of translational efforts, with the "development" in R&D. To be sure, R&D people are important elements in a product development organization—as are development scientists (which, depending on the nature of the products, can include biologists, chemists, physicists, computer scientists, engineers, or others) and participants with experience and expertise in marketing, manufacturing, quality assurance,

Strong opposing currents—swim against the stream with strength, organization, and courage

- Corporate bureaucracy
- Not enough money
- Not enough people
- Not enough time
- No senior management representation
- Lack of senior management commitment
- Physical separation of team members
- Inadequate technology base or core competencies
- Bad attitude about regulatory and quality requirements
- Management turnover
- Unrealistic expectations
- Unclear business objectives
- Reorganization
- Restructuring
- Reengineering

Figure 13.3 Internal impediments to medical product development that are not usually controlled or significantly influenced by a product development organization (salmon swimming upstream analogy).

Rapids and waterfalls—avoid or know ahead of time how to negotiate

- Competitors (some)
- Reluctant customers
- Decreasing product life cycles
- Premature obsolescence by new technologies
- Unclear fit with customer/market needs
- Negative image from past product problems
- Poor rapport with FDA
- Unreceptive marketplace
- Vendor/supply problems

Figure 13.4 External impediments to medical product development that can be controlled or influenced by a product development organization (salmon swimming upstream analogy).

Grizzlies and other predators—be aware and be prepared

- Vague/changing FDA requirements
- Differing global requirements
- Outcomes requirements
- Managed care
- Other unpredictable new health/medical issues
- Competitors (some)
- International cultural biases
- Emerging or new diseases
- Aging/expiring patents
- Healthcare reform

Figure 13.5 External impediments to medical product development that are not usually controlled or influenced by a product development organization (salmon swimming upstream analogy).

- Commitment to quality
- Cross-functional participation
- Technology assessment capability
- Concurrent (parallel) development approach
- Group knowledge of regulatory issues
- Upper-level management representation
- Immediate access to information resources
- Clear understanding of where the buck stops

Figure 13.6 What a product development organization requires.

regulatory affairs, preclinical testing, clinical evaluations, new business development, and other functions. Product development is a cross-functional activity, and as such requires the involvement of a cross-functional group sharing the same goals: identification, development, and launch of new products. This does not at all mean that there must or even should be a separate product development department within a company or academic institution (although separate product development departments can work very well in industry). What it does mean is that without the participation of

individuals with a variety of specific functional abilities—that is, without involvement of a cross-functional group—healthcare product development efforts will be next to worthless. This is the most fundamental requirement.

By the way, one functional area that is often overlooked or underestimated is responsibility for and capability of assessing technology. It is an easy and mistaken assumption that conventional new business development departments, including academic technology transfer divisions, take care of this. Many business development associates are splendid at identifying opportunities but lack the knowledge of the scientific, regulatory, and market nuance issues that profoundly affect the opportunity. To have someone with these skills working with business development associates or, indeed, working in the capacity of business development, makes for a much more powerful and effective tool when it comes to searching for new opportunities.

Some companies, and most academic institutions, do not have resource representation in all of the functional areas that may be critical to the products they are trying to develop. If the required skill sets are not on hand, or if certain skills are needed only infrequently, collaborators and consultants can provide a satisfactory solution. Consultants may be independent and from the outside, they may be internal to a company and available ad hoc to various product development initiatives, or they may be available through lending out of expert associates of affiliate companies. The important thing is to have people with the necessary skills readily available and involved in the new product development efforts. The composition of product development groups will vary based on whether the innovations originate in-house in a company or in an academic institution or other research organization, and on the nature of the collaborating parties. But the overall requirements of screening to select the best possibilities from concept to commercialization are the same.

Much has been written and discussed in recent years about the advantages of concurrent engineering in product development. Simply put, *concurrent engineering,* or *parallel development,* refers to the simultaneous as well as sequential integrated execution of tasks by various functional participants in the product development process. This approach differs from the "handing-off" system in which one function—for example, R&D—does what it considers its part and then hands off the project to another group, such as manufacturing, which may then hand off to regulatory affairs, which hands off to marketing, which hands the responsibility over to sales. Concurrent engineering seems to work best. Some companies, however, prefer to employ the sequential handoff approach, often because of deeply entrenched habits and history. Medical product development can succeed in this environment if there is sufficient cross-functional project

planning and if documentation and progress are frequently reviewed by a responsible cross-functional group.

Two other aspects that are very important to successful product development are convenient access to a well-stocked electronic library with subscriptions to as many relevant periodicals as possible, and the requirement for all participants in the product development organization to understand regulatory issues and quality standards. It is perplexing that so many otherwise respectable healthcare manufacturers cut costs by eliminating subscriptions and access to document search and retrieval resources. If something sparks in your mind and you need information now to satisfy the itch, you need the information *now.* In a day or two, the itch will be gone or you'll have forgotten why you were so interested in the first place. Momentum will be lost and opportunities will vanish.

A word about regulatory and quality affairs: They are inextricable and they are everybody's business. The medical products industry is too sensitive to regulatory issues to assume that product development can proceed smoothly as long as a regulatory affairs specialist is nominally on hand. In fact, the performance of that specialist will suffer unless everyone involved with product development is cognizant of the regulatory environment and understands, for example, the difference between guidelines and regulations. Organizations also may have misconceptions about quality functions. Quality is not just an attribute of a finished, manufactured product indicating that it meets some set of product specifications. It can not be simply considered a post-development issue, and personnel involved in quality functions must be included in product development activities. Quality has to be built into a product by being incorporated beginning with the earliest stages of the product development process. Remember, domestic and international standards now require that quality systems include the design phase of product development.

Finally, in the seemingly never-ending quest to turn around a lagging or failing business, companies are periodically and regularly reinventing, reorganizing, restructuring, and reengineering. Such companies are very likely struggling because they are not developing any new products or they are developing the wrong products. Both problems are indicative of inadequate, dysfunctional, or absent product development processes, product development organizations, and product development support. Yet, surprisingly, the revised organizational structure may end up having no upper management representation for product development. In the realm of FDA-regulated medical products, product development needs a champion at a level that is heard and that carries influence. Development is less effective if upper management responsibility is left to another specific functional representative who has all of the company responsibilities for that

particular area to worry about, or to a nontechnical business generalist who has to put out daily fires and worry about the quotidian bottom line. To remain or to become known for excellence in product development, a medical products company should be eager to show its commitment and support through high-level management responsibility and representation for product development. It is as important for that responsible individual to be able to participate firsthand, on a daily basis, with other functional and business executives in discussions of business issues and strategic direction as it is to be an advocate for the product development organization and product development process. It makes a great deal of sense to have intimate management leadership provided by someone who can concentrate on creating tomorrow's business and who is not preoccupied with all of the distractions of managing and running today's business.

With a talented and trained product development organization in place, a medical products company will be in a position to implement product development planning. The first important steps will have been taken for providing a steady stream of profitable new products.

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14

Components of Product Development Planning

The Product Development Process

Begin at the beginning . . . and go on till you come to the end: then stop.

—Lewis Carroll

The medical product development process is one of the four integral components of product development planning (see Figure 14.1). It is also the component of product development planning that is most firmly grounded in the present because its implementation requires the

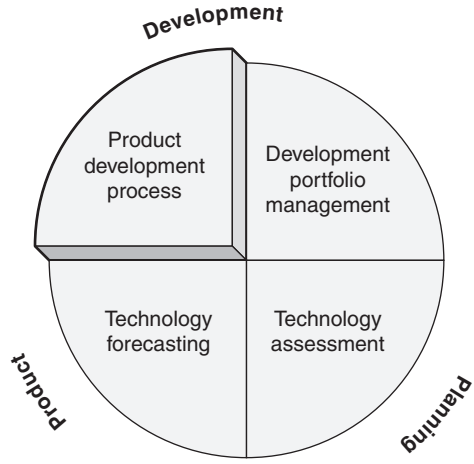


Figure 14.1 The product development process is an integral component of product development planning.

existence of one or more ideas or opportunities on which a product development organization can act.

Product development is generally thought of as a series of steps or stages, beginning with a product idea or opportunity and ending with the launch of a new product. Often, an analogy is drawn to human development in utero, with conception, gestation, and labor and delivery representing the stages of product development. While valid in some respects, this analogy neglects some very important points.

Despite the division into stages and trimesters and such, in utero development occurs through a continuum of processes and doesn't happen in a saltatory fashion. Although conception may be the official initiating event, it is preceded by an actionable idea and it must be enabled by physiologically capable bodies. If, following conception, a complex myriad of interacting factors work together in concert, gestation proceeds and a healthy baby is born. But to remain viable, the baby requires nurturing, monitoring, and support.

The product development process is also a continuum of activities, starting with the light bulb that is switched on in someone's prepared mind (an occurrence enabled by intelligent and supportive management) and ending with the early support activities that follow the introduction of the new product into the marketplace. In between, a complex myriad of interacting factors working together in concert somehow has to take place. It is the responsibility of the product development organization to make sure that this happens.

For the sake of convenience, it is helpful to identify some of the infinite number of steps that make up the continuum of product development, from bench to bedside:

- Idea generation
- Concept evaluation
- Feasibility testing
- Product definition
- Design development
- Risk analysis
- Design optimization
- Prototyping
- Confirmative testing
- Pilot production

- Scale-up
- Production
- Launch
- Follow-through

The objective of establishing a product development process divided into discrete stages is to (1) provide discipline and consistency for internal review and portfolio analysis, (2) establish a product development system, focused on quality, with formal design review milestones to comply with design controls requirements/recommendations of FDA GMPs, and (3) facilitate eventual marketing of developed products outside of the United States by meeting international standards for design control. There is no reason to duplicate efforts, so a well-constructed product development process will accomplish all of the objectives simultaneously. As a bonus, implementation and action on such a process will greatly improve the likelihood of developing a product that is right for the customers, right for the company, cost-effective, manufactured with quality, and free of design defects. And once the process is understood, accepted, and supported by those involved in product development and by management, shortened development time will be a reality.

It wouldn't be realistic for most product development organizations to employ a process with as many stages as indicated above. Some of these elements tend to fall together into natural groupings. The number of groupings and the elements included in each can be customized according to the nature of the products being developed by the organization. Think about what makes sense in terms of review frequency for the protection of the patients, the security of the company, and the satisfaction of FDA. If a very simple product is being developed, if it is not unique and is fabricated from common and conventional materials, and if the company has the appropriate core competencies to develop and make the product, two or three reviews before launch might be adequate and acceptable. If the product idea involves complex, largely untested technologies and carries with it a high degree of financial, technological, regulatory, market, or safety risk, 10 formal reviews might actually be a good idea.

For some Class II and most Class III medical devices, and for drugs and biologics of comparable complexity, it would be wise to use at least six product development stages along with five reviews, three of which are formal design reviews (see Table 14.1). Remember that for medical devices the schedule for design review and the output of these reviews will become part of the company's permanent design control process and file to demonstrate adherence to QSRs (that is, device GMPs). For the purpose of illustration

Table 14.1 Six-step healthcare product development process.

Product development phase	Review at phase completion
1. *Discovery*: generation of ideas and search for opportunities	Management approval
2. *Feasibility*: concept testing and evaluation of likelihood of success	Design review committee/ management
3. *Optimization*: development and refinement of product design	Design review committee: formal design review
4. *Demonstration*: confirmation of safety and effectiveness	Design review committee: formal design review
5. *Production*: scale-up to commercial-level manufacturing	Design review committee: formal design review
6. *Launch and follow-through*: introduction into market and support of the new product	

and future discussion, then, we will consider a generic six-stage medical product development process.

- Stage 1—discovery
- Stage 2—feasibility
- Stage 3—optimization
- Stage 4—demonstration
- Stage 5—production
- Stage 6—launch and follow-through

At the end of each stage, a review system functions as a screen or filter, allowing the projects with the greatest potential to pass through to the next stage while excluding those with less potential. Figure 14.2 illustrates the application of this process to the product development funnel model.

STAGE 1—DISCOVERY

The unrestrained generation and accumulation of ideas takes place during the *discovery* stage. It is a time for exploration, ideation, suggestion, brainstorming, and investigation. Each idea is a potential new product concept. The ideal situation for a product development organization to be in is to

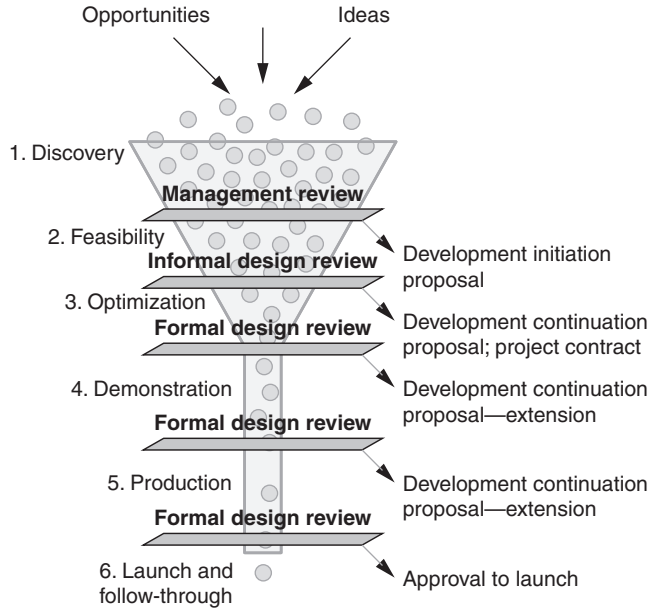


Figure 14.2 The product development process.

have a surplus of ideas in relation to the number of projects it can actually pursue. It is through discovery that possibilities enter the wide, open end of the hypothetical product development funnel.

Conventional product development literature frequently recommends determining what customers' needs are, then seeking ideas that might provide solutions. Or conventional approaches may insist that all exploratory searches start with an analysis of the industry under consideration for a product entry. It is frequently suggested, too, that all ideas sought should be compatible with core capabilities, such as specific scientific or manufacturing expertise. In the medical products industry, strict adherence to these tenets may be unwise. It constrains one to view the future through the veil of a preconceived present.

In the first place, customers don't always know what their needs are. This goes for both patients and medical professionals. As consumers, we should all be able to think of some product or technology that has entered and changed our lives greatly for the better. Before that product became available, we had never given a thought to the technology or to the need it would serve, but now we wonder how we ever got along without it. Today, we may recognize tablet computers, electronic networking, and cell phones

as falling into this category of life-altering advances—known as *disruptive technologies.* In the past, electric lights and penicillin were disruptive technologies. If a product development organization is going to beat its competitors to the future, it has to take off the blinders and be receptive to ideas and opportunities that may, at first blush, seem outlandish, inappropriate, or inconsequential. Those involved in product development must be prepared to lead customers into the future by offering products for which those customers might not, on their own, have recognized or articulated a need.

By collecting ideas only within the context of an industry analysis, a medical products company can be fairly sure that it will be left behind, buried beneath the dust kicked up by open-minded competitors with foresight as they race to the market with successful new products. Consider the dizzying advances in diagnostic abilities, recombinant genetic technology, tissue engineering, microsurgery and minimally invasive surgery, robotics, and the stunning challenges presented by reemerging or newly emerging or unidentified diseases, not to mention politically and economically sensitive issues such as healthcare reform and managed care. Anyone presuming to be able to get to the future with medical devices, drugs, or biologics products by using ideation based on the industry and market as we now know it, or as we might anticipate it to be in the short-term future, belongs in a different business.

Finally, the admission of an idea into the discovery stage should not be predicated solely on the basis of the core competencies of a company—even though core competencies are an important element in product development planning. Successful companies do not remain static. New competencies can be built, acquired, or contracted if an idea or project is important enough.

Remember, just because an idea is in the pool in the discovery stage doesn't absolutely mean it's going to become a project. There will be ample opportunity to apply restrictions, hurdles, and other screening procedures. A seemingly inappropriate idea may spark another idea or may set off a chain reaction of ideas, and a terrific new product opportunity could be the result.

Ideas can include the likes of novel concepts, suggestions for differentiated line extensions, suggestions to go after or take advantage of licensing opportunities, and proposals for acquisitions. Ideas may come from just about anywhere—from R&D, marketing, or any other company group; from customers and competitors; from technical and patent literature; from technology transfer groups; from academia; from newspaper and magazine articles; from conventions, symposia, and professional meetings; from one's children; from dreams. The ideas are assessed according to predetermined and agreed-on criteria for advancement to the next stage.

Examples of evaluation questions and criteria used in this initial opportunity screening process are shown in Figures 14.3 and 14.4. The criteria must be established by management or in conjunction with management to assure compatibility with strategic business plans. Not all of the questions will be answerable at this stage, but a sufficient number of key answers will be required to present a convincing recommendation for advancement. If there are too many blanks, more homework should be done. Those ideas that do not pass through the screen can be left in the pool to be reevaluated in the future, passed on to affiliate companies, or discarded.

- What is the product concept?
- Who are the main customer groups?
- Who is the end user?
- What is the expected function of the product?
- What customer need does it fill?
- What other products fill this customer need?
- Who are the competitors?
- What are the unique features of the product concept?
- What is the domestic market potential?
- What is the foreign market potential?
- What are projected sales in year one?
- What are projected sales in year five?
- What is the projected gross profit?
- What investment is required?
- Is the technology new?
- What is known about safety?
- What are the safety concerns?
- What would the customer pay for the product?
- What is the patent status or opportunity?
- What is the license status or opportunity?
- What is the projected development time?
- What is the anticipated regulatory pathway?
- Are clinical studies required or likely?

Figure 14.3 Questions to consider when evaluating ideas.

Based on business strategy and philosophy, the following should be determined:

- Targeted customers and end users
- Minimum domestic market potential
- Minimum international market potential
- Minimum annual sales
- Maximum investment
- Minimum acceptable gross profit
- Acceptable risk versus benefit
- Need for technology or application to be proprietary
- Requirement for exclusivity in marketplace
- Acceptable regulatory pathway
- Need for fit with existing competencies

Figure 14.4 Examples of idea evaluation criteria.

The output of the discovery stage is a *development initiation proposal*, which is essentially a petition to take a given promising idea into the next stage of product development. The development initiation proposal should contain enough information from relating the evaluation questions to the evaluation criteria to convince management that the specific idea is worthy of being made into a project and that an investment should be made to proceed. Occasionally, a breathtaking idea or opportunity is unearthed that does not fit in with the defined business strategy, but it looks like a real star. In such cases, it is the obligation of the product development organization to make the opportunity known to management. Business plans and direction can be modified if the potential is great enough.

At the conclusion of the discovery stage, management approval to continue constitutes an agreement to commit a defined quantity of human and financial resources to take the new project through the feasibility stage. Here, *management* refers to the level or structure within a given company that retains the authority to approve the required level of resources to proceed. Thus, the narrowing of the product development funnel begins.

STAGE 2—FEASIBILITY

Stage 2 of the product development process begins with the identification of a project team and team leader. The nature, size, structure, and

philosophy of a company may dictate who identifies the team, what functions are represented on the team, who selects the team leader, what the role of the leader is in shepherding the project through the various stages of development, and whether the team is self-directed, dedicated, or shared. There is no question, though, that the same cross-functional team—all trained in the product development process and familiar with regulatory requirements—should be involved through all stages of a given project. Use of the title *team leader* sometimes causes envy, friction, lack of buy-in among team members, confusion about responsibility and accountability, or misgivings about who will be rewarded for a successful project or held responsible for failure. A more sociologically neutral term such as *guide*, *facilitator* or *steward* may be less inflammatory and thus more effective than *leader.*

Feasibility involves concept testing in terms of market opportunity, customer acceptance, technological readiness, basic proof of principle, materials selection, manufacturability, packaging and sterilization options, stability and probable shelf life, and patent issues. The questions asked of an idea in the discovery stage are reconsidered in greater depth during the feasibility stage. If at all possible, an early prototype or mock-up should be evaluated to demonstrate the reality of efficacy, although it is sometimes necessary to base the initial assumptions of safety and/or effectiveness on theory. Now is the time to clearly articulate the product concept and design goal.

During this stage, the testing plan is determined, the desired promotional claims for marketing are defined, the regulatory strategy is set, and a detailed budget reflecting the investment necessary to take the project through to completion is prepared. In other words, the future path of the project is defined. With the availability of a variety of project management software packages, it is nearly inconceivable to think of engaging in product development without computerized assistance. The significant steps in the product development stages that follow feasibility are subject to design controls as required by FDA and by international quality and regulatory organizations. The software packages can generate a project plan that will form the basis of the design controls system.

At the conclusion of the feasibility stage, the project team determines the likelihood of successful execution of the project and makes a recommendation, detailed in a development continuation proposal, to the design review committee, who will be the group responsible for design review as required by design controls regulations.

The original management group responsible for approving the development initiation proposal, if different from the design review committee, may elect to have veto power based on business reasons that transcend the

reasons that the project team will present to either continue with a project or to kill it. The product development funnel is further narrowed.

If a project receives approval to be taken into stage 3 (optimization), a project contract between management and the project team is advisable. The project team agrees to develop the product on a timeline that is based on real information and that is acceptable to the team and to management. The team understands its obligations and recognizes that reward and recognition—or the absence thereof—depend on adherence of the team to its proposal and the timely attainment of milestones. For its part, management agrees to provide the needed financial, moral, and labor support, and provides the team with the assurance that, during the next stage, the plug will not be pulled on the project—at least not for spurious reasons.

STAGE 3—OPTIMIZATION

Optimization means refining the product design so that the product meets expectations for function, form, and performance. The activities involved in optimization, the results of these activities, the recommendations made by the project team, the reasons for the recommendations, and the results of the design review must be documented.

During the optimization stage, the design is completed, and product attributes and product specifications are further defined, refined, and frozen. Therefore, elements important to the user/product interface—that is, human factors—must be explored and addressed. Final packaging and sterilization requirements are identified, and required materials for manufacturing and packaging are procured. The investment in any necessary new machinery, equipment, or tooling is made. Prototypes are fabricated, shelf-life studies are initiated, and all required preclinical safety and efficacy testing is conducted. If clinical testing on human subjects will be required for product approval, an IDE or IND is prepared using the data generated during optimization. Depending on the product, and if the product does not need clinical testing requiring an IDE or IND, it might be possible to prepare and submit documentation for clearance or approval to FDA at the end of this stage.

Depending on how the tasks and assessments progress during the optimization stage, the project team will either recommend that the project be killed or it will submit an extension of the development continuation proposal to the design review committee. Design review at the end of the optimization stage will ascertain whether the product performance meets product requirements, whether the product meets customer needs, whether cost and price are acceptable, and whether there are any issues with safety,

effectiveness, reliability, or ease of use. If a project makes it through optimization, and if the right assessments have been made and documented, the probability of an eventual regulatory approval or clearance is high. The product development funnel has become very narrow and very focused.

STAGE 4—DEMONSTRATION

Demonstration includes pilot-scale manufacturing and validation of the manufacturing process to prove that the product can be made as anticipated. The product made during this stage is evaluated in clinical studies (if clinicals are required) to demonstrate clinical safety and effectiveness when the product is used as intended.

Not every project will go through the demonstration stage; some will move directly from optimization to production. Demonstration is appropriate if it is desirable for a product to be launched from a pilot manufacturing facility—perhaps while a larger facility is being constructed. This stage may also be applicable if lengthy clinical studies are required, especially if there is any question regarding the significance of the outcomes of the clinical studies. In this case, investment in additional facilities can be delayed until there is greater certainty of clinical success and regulatory approval. If the product from this stage will be launched or evaluated in clinical studies, the manufacturing process must meet GMP requirements, and the pilot-scale product must be validated to ensure that it meets specifications and all safety and efficacy requirements. If the required regulatory submissions were not made during stage 3 (optimization), they are prepared and forwarded to FDA.

If all goes well with the demonstration stage, the project team will probably recommend taking the project into the next stage. The project plans may call for a launch from pilot facilities, in which case the project will move to stage 6 (launch and follow-through), or to stage 5 (production) and stage 6 simultaneously. In any case, an extension of the development continuation proposal will again be presented to the design review committee.

STAGE 5—PRODUCTION

Production is the final, scaled-up manufacturing stage for commercial production of the product. The manufacturing process, equipment, and facilities must be validated and must comply with GMP regulations. The product from the production stage must be evaluated to assure that it meets

specifications and will be safe and efficacious in use. If regulatory approval or clearance is in hand, the design review committee will be requested to approve launch of the product.

STAGE 6—LAUNCH AND FOLLOW-THROUGH

While many of the individuals involved in the product development process may regard their work as being completed, it is not so. The fruits of their labor are visible and tangible evidence of a successful development plan, but the success of the product is still at risk. Clearly, team members from marketing and sales will be especially active. But operations and quality assurance team members must monitor the manufacturing process and the product being produced, and R&D team members should provide support to the field through educational programs and by supplying answers to customers' technical or medical questions. FDA may require post-marketing surveillance of certain products as a condition of their remaining on the market. This requires substantial regulatory and medical or clinical affairs activity.

There is, of course, no guarantee that a project emerging from the process described will live up to its expectations and be immune to defects, adverse reactions, or recalls. But with a clever and dedicated product development organization, a supportive and enthusiastic management structure, and diligent adherence to the quality-based project plans and teamwork, the new project has an excellent chance to be a winner.

15

Components of Product Development Planning

Development Portfolio Management

More is in vain when less will sustain.

—Attributed to William of Ockham (paraphrased)

When investing in the stock market to make money over a long period of time, it is customary to maintain a stock portfolio. The portfolio may have a mix of growth and income investments, blue-chip and start-up stocks, and so forth. The balance of the investments in the portfolio is tailored to reflect the immediate needs as well as the future financial goals of the particular investor. Similarly, companies maintain a product portfolio, generally consisting of a mix of different types of products—some are old standbys with strong name-identity value, some are modifications or new applications of the traditional products, and some are new to the company or perhaps even to the marketplace. The mix of product categories reflects the business position of the company, as well as its goals. Companies specializing in products with short life cycles—those easily and quickly obsolesced by competitive activity or rapidly changing customer needs—require a higher ratio of new products in the product portfolio than companies whose products have relatively long average life cycles. Maintaining the proper product mix in a product portfolio helps a company minimize long-term risk.

In a parallel fashion, a successful product development organization must maintain a portfolio of development projects. Development portfolio management is an integral component of product development planning (see Figure 15.1). Development portfolio management maximizes control and minimizes risk in keeping a company's strategy for new products compatible with its business needs, objectives, and resources. It can ensure a continual flow of promising ideas into the product development funnel, provide guidelines for converting ideas into projects, track and monitor

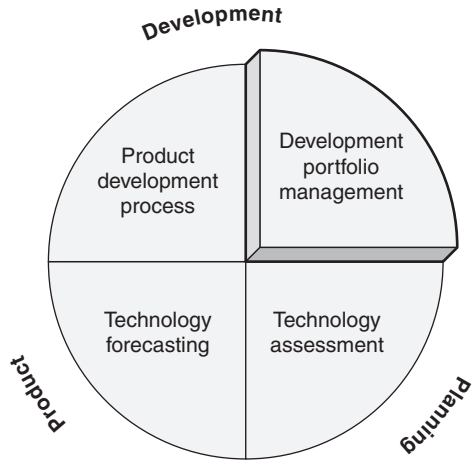


Figure 15.1 Development portfolio management is an integral component of product development planning.

progress of active projects, and define milestones for continuing projects versus killing projects as they progress through the development funnel. Thus, managing the development portfolio provides a link between opportunities, development projects, new products, and business strategy.

Development portfolio management requires (1) establishing a model for portfolio assessment or analysis, (2) the existence of and adherence to a defined product development process, and (3) integration with formal technology assessment activities.

Portfolio assessment will reveal the existent technical strategy of the company and measure how well that strategy is integrated with the business. Implementing a defined product development process will provide the foundation for a company to be successful in developing projects in the portfolio and bringing new products to market. A formal technology assessment program will assure that the mid- to long-range technical strategy is aligned with the business strategy. These three elements should be regarded as interdependent and inextricable from development and technology management in product development planning.

The purpose of product development portfolio assessment is to:

- Identify development programs and activities
- Categorize development programs and activities
- Guide the development programs

- Provide a fit and value framework for evaluating new ideas/new project opportunities
- Guide acquisition, licensing, and divestiture activities
- Provide measurements that allow comparisons and benchmarking
- Evaluate the fit of the development programs and activities with the overall technology and business strategies of the company

There are many models used in business for assessing product or project portfolios. A product development organization may either adapt one of the existing models to product development activities or create a new, customized model.

Portfolio assessment captures the position of a given project relative to other projects in the overall context of the business strategy. Every resource-requiring product development project or opportunity should go into the portfolio. Each project is examined in terms of a variety of attributes and risks. The examination criteria mesh with those used to evaluate new ideas and to determine whether a project is allowed to advance through the development funnel, as presented earlier in this book. We see now that there is an apparent "chicken or egg" conundrum. Which comes first—a model for portfolio assessment or a product development process? Since they can't spring into existence simultaneously and fully formed, the most empirical and practical approach would be to define a product development process first. The experience gained through applying discriminatory criteria to individual projects as they wend their way through the development phases (discovery, feasibility, optimization, demonstration, production, launch, and follow-through) will bring focus and relevance to elements of portfolio assessment.

The framework used to assess ideas, projects, new-to-the-company product opportunities, and future new product possibilities should be based on a group of essential core qualities applicable to all four components of product development planning. Some examples of core qualities are given in Table 15.1. This type of review may be adapted to provide information that is primarily qualitative, semiquantitative, or highly quantitative. Depending on the component of product development planning to which the basic evaluation scheme will be applied, certain issues will become more or less important, and different assessment issues may be added to or deleted from the scheme. It is important to identify the most important issues and to consider them in a way that will allow information from one stage of product development planning to flow smoothly into another

Table 15.1 Framework for basic assessment of ideas, projects, and future opportunities.

Issue	Status	
Customer/market need	Now met	Unmet
Market opportunity	Small	Large
Market growth	Low	High
Fit with business strategy	Poor	Good
Profitability	Low	High
Profit impact on company	Small	Large
Competition	Strong	Weak
Patent position/exclusivity	Weak	Strong
Time to commercialize	Long	Short
Company technological capability	New	Existing
Regulatory obstacles	Difficult	Less difficult
Investment required	High	Low

stage. Before engaging in any type of assessment, it is critical to first clarify the customer and the end user, and the nature of the clinical need that is expected to be addressed.

Portfolio assessment requires some system of data collection, matrices, and measurements. The approach can range from very straightforward and spartan to enormously complex and byzantine. There is no intrinsically right or wrong way to do it. If a product development organization has the opportunity and flexibility to define its own model, as opposed perhaps to using a corporate model, the most important elements would be understandability, ease of use, meaningfulness of data, and consistency of application. These qualities are very specific to particular businesses, cultures, and organizational structures and, consequently, work best when they are at least somewhat customized. Portfolio analysis is not a one-size-fits-all process.

A key to portfolio assessment is mapping. *Mapping* is a tool in which individual components of some collection—such as products or projects—are evaluated according to various sets of characteristics. Mapping allows a visual presentation of relationships between projects, and between projects and the evaluation criteria. There is no limit to the nature and number of qualities that may be evaluated, so selectivity must be based on the objectives and strategy of the company and the product development

organization. Project information, for example, can be presented in ways that range from primarily qualitative to highly quantitative. However, important elements to capture in terms of project evaluation include:

- Degree of correlation of each project with short-, mid-, and long-range business strategy
- Customer need/market need
- Cost to complete development and launch
- Category of project
- Developmental stage of project (its location in the funnel)
- New product launch year
- Projected sales
- Resource requirements
- Technical feasibility
- Projected profit

Data and information can be arrayed in any manner that provides an informative visual presentation, including bar graphs, line graphs, pie charts, and so on. For the purpose of illustration, consider a very simplified boilerplate matrix that classifies attributes into two categories along each axis, as shown generically in Figure 15.2. The attributes evaluated reflect anything relevant to the business, the business strategy, and to established regulatory and quality requirements. Examples would generally include reference to customers, markets, technological feasibility, costs, time to commercialize, and so on. In other words, we would examine the core features in the evaluation framework shown in Table 15.1, with certain modifications particularly applicable to portfolio analysis (see Table 15.2). In this simple model, the status of each attribute is categorized into one of two complementary extremes, such as low/high, old/new, same/different, and weak/strong. Of course, the maps that are generated must then be interpreted. Depending on the interpretation, an action plan can be defined and implemented. Figure 15.3 shows an example of a possible interpretation based on quadrant location, using an analogy to a poker game.

A look at how a new product development organization for a fictitious company might map projects should further illustrate the concept of mapping. One type of map that is useful in classifying projects according to new product categories plots the market addressed with regard to the company (current versus new) against the technology requirement with regard

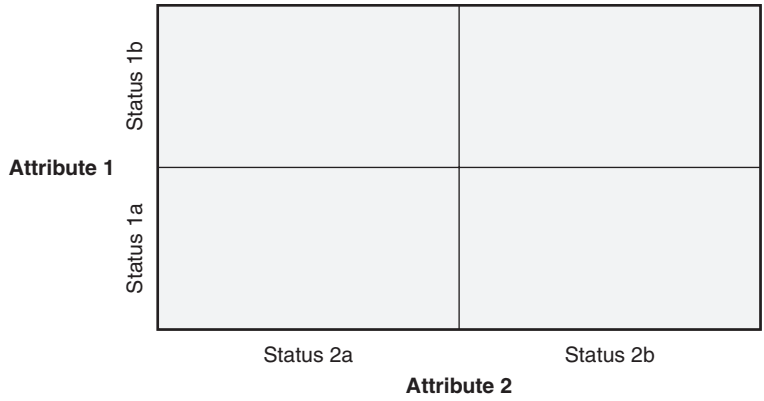
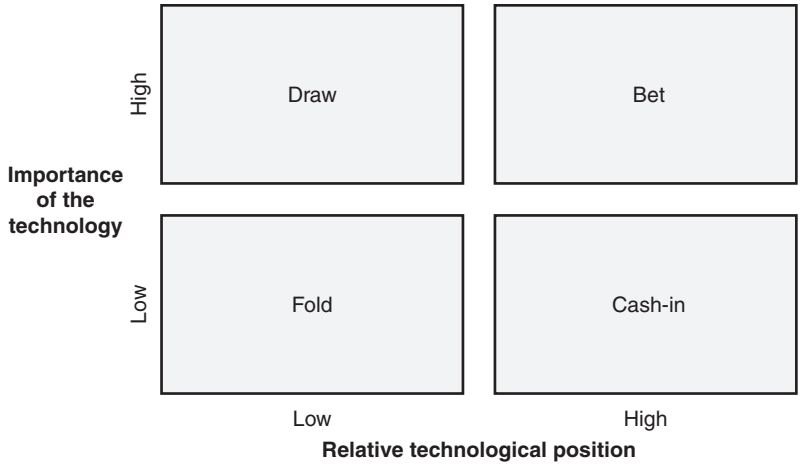


Figure 15.2 A simple portfolio map matrix.

Table 15.2 Additional characteristics for project mapping.

Attributes	**Status pairs**	
	(a)	(b)
Sales (year 1, year 5, and so on)	Old	New
Technological risks	Same	Different
Manufacturability	Yes	No
Ease of use	Weak	Strong
Outcomes advantages	Easy	Difficult
Global opportunities	Clear	Unclear
Return on investment	Certain	Uncertain
Fit with core competencies	Small	Large
Stage of development	Early	Late
Requirement for new process development	Low	High
Competitive advantage		
Product life span		
Gross profit		
Financial risk		
Probability of on-time development		
Probability of successful development		
Availability of required resources		



The four quadrants are described as follows:

- **Bet.** The company is in a technologically excellent position in a business segment where that technology is important: objectives should be to sustain and increase competitive advantage. This is the business where one must commit oneself to the newest equipment.
- **Draw.** The company is in a borderline position. One needs to make two decisions: either bet against the competition and invest to attain a leadership position, or develop a plan to disengage from, or even abandon, that technology and invest in more lucrative areas.
- **Cash-in.** The company is in a technologically strong position, but the technology where it excels is not really important in marketplace terms. This situation occurs most often in a rapidly changing industry, such as electronics or engineered plastics, where existing technology is continually being supplanted by new techniques. Technologies underlying aging product families (frequently a company's original product lines) tend to lie in this quadrant too.
- **Fold.** The company is technologically weak in an unimportant field. If heavy investment has taken place, this money may have to be considered sunk costs. If not, then a financial redeployment strategy is essential (and the sooner the better).

Figure 15.3 An example of a technology portfolio matrix.

Source: Arie P. Nagel, "A Framework for Technology Strategy" in *Product Development*, edited by Margaret Bruce and Wim G. Biemans (Chichester: John Wiley & Sons, 1995): 69. Copyright © 1995 by John Wiley & Sons, Ltd. Reprinted by permission of John Wiley & Sons, Ltd.

to the company (current versus new) (see Figure 15.4). Assume, for the sake of the example, that a hypothetical company has six development projects, each represented by a different letter: A through F.

Figure 15.5 shows how these projects sort out when mapped to reflect the market addressed versus the technology requirement. It shows a clustering of projects that address the fictitious company's current market and that can be accomplished with the company's current technology. There are no projects that address a different market and also involve a technology that the company does not currently have. What the map shows, then, is that

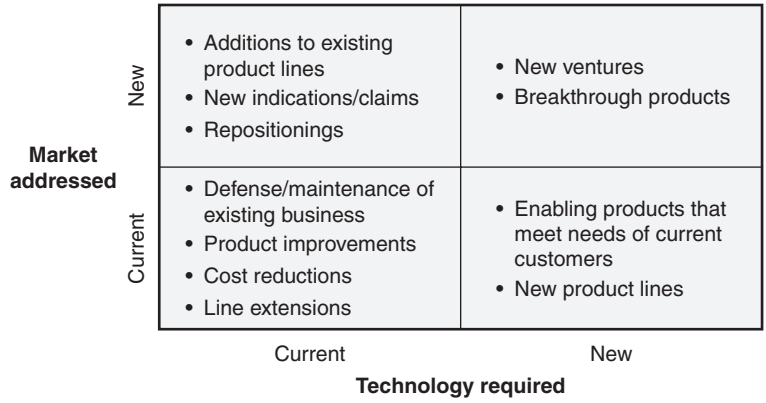


Figure 15.4 Portfolio map matrix showing types of projects.

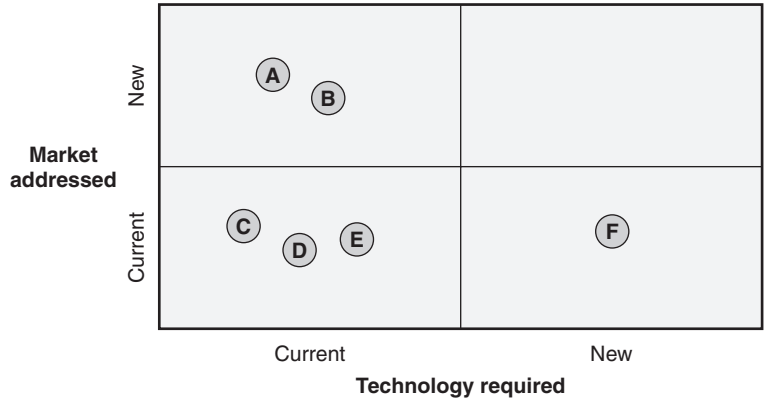


Figure 15.5 A project map for a fictitious company: is it good or bad?

half of the projects in the development portfolio of the company relate to doing little things with existing products—perhaps size changes, repackaging, or cost-improvement efforts. One-third of the projects involve relying on the current technology to somehow address a different market—perhaps through adding new claims or new indications for use to a current product. The remaining project involves a new technology to address the current market—possibly a licensing arrangement for a previously competitive product. Conspicuously absent are any projects that would expand both the market and the technological capabilities of the company, which could include projects that are—in addition to being new to the company—new to the market or even new to the world.

The next issue that must be considered is whether to interpret this mix of projects as good or not good. In order to do this, there must be some concept of what would constitute the ideal maps for a given company. Reality would then be compared to the ideal to provide direction to the development strategy. Although there are no one-size-fits-all-companies ideal maps, there is clear reason to avoid projects that fall into a quadrant that encompasses two negative elements, such as small market opportunity coupled with poor fit with business strategies, or something falling into the "Fold" quadrant defined in Figure 15.3.

For some companies, notably those adverse to risk-taking but satisfied with running in a maintenance mode, the assortment of projects seen in Figure 15.5 may be acceptable. Companies interested in extensive and rapid growth, though, would recognize the need to fill the empty quadrant and reassess the wisdom of having a large number of low-risk projects.

The most important purpose, by far, of engaging in the exercise of portfolio assessment is to assure that the product development activities of the company are integrated with the business. Consequently, it is possible to evaluate the meaning of the maps only if they are considered in context with the specific business. This means that development portfolio assessment is not an exercise just for scientists, and it is not an exercise just for marketing people. It must be a cross-functional activity and, at some point, must include individuals with significant management authority and detailed knowledge of where the business wants to go and how much it is willing to invest to get there. It may not be logistically feasible for all product development team members to participate in portfolio assessment, but a significant number of those participating in portfolio assessment should be involved in product development.

Individuals involved with portfolio analysis must be able to make recommendations and decisions within the context of the business strategy. During review of the projects and portfolio, decisions will have to be made whether to continue or discontinue each project. The fit of each project with

requirements for projected sales potential, business compatibility, technological feasibility, and time and resource requirements, for example, must be constantly challenged.

With a few exceptions, there is no particular quadrant within a given map in which a company must feel obligated to play, nor one from which it is mandatory to stay away. The "play or stay away" decision depends on where the company envisions itself at present and in the future. Placing projects in a quadrant that reflects high investment and low return might be an obvious situation for company ABC to avoid, but might make sense for company XYZ if it would provide dominance or control of a market in which XYZ is already a player.

Another thing to bear in mind is that for portfolio assessment to be useful, it must be an ongoing exercise. Development portfolios with many projects generally require more frequent analysis and review than portfolios with fewer projects. The frequency of review should also reflect the vibrancy, or conversely the torpor, of the company, as well as the number of projects in the portfolio. Business strategies evolve and change. Six months after company XYZ has committed to a high investment/low return project in order to gain market dominance, the controlling management of XYZ might decide to exit that market entirely. Project continuance and resource allocation would obviously have to be readdressed, and the configuration of the portfolio would be altered.

Similarly, there can be changes in the competitive environment that affect the value of a particular project regardless of its position on the maps. If ABC gets clearance or approval from FDA to introduce a new product, for example, it can suddenly become very important for ABC to prioritize a similar project that doesn't look particularly attractive based on most attributes, but which can be developed in a very short time and provide stronger name recognition for ABC in that market. Meanwhile, company XYZ, which also had been nurturing a similar project, might decide to kill the project since its strategy does not include being a me-too player in that market. If, on the other hand, ABC had failed to gain FDA clearance or approval, XYZ might well have accelerated the project in hopes of now being the first to market.

In addition to the right-for-the-company categorical mix of projects, mapping should include presentations of the stage of development of each project and an indication of when the resulting new product will be launched. Remember, the time remaining before launch is not necessarily reflected by the developmental stage of a project. A pharmaceutical or Class III device requiring new clinical trials may be in a relatively advanced (late) stage of development but still require years before product launch. By comparison, a line extension for a Class I or Class II device might be in

the earliest developmental stage—with an idea approved but without any additional follow-up—yet this early-stage project could lead to a product launch in far less than a year. It is important to identify gaps in timing, as well as in project type. One can become very creative in combining representations of three, four, or more product characteristics in one map. Use of color and the depiction of individual projects in different shapes and sizes to reflect such things as developmental stage and sales potential are tricks that can be used.

Some organizations, whether they use primarily qualitative or highly quantitative maps and matrices, assign weight to the factors being considered in portfolio assessment, according to a perceived importance to the business. Since it is clear that, in the final analysis, subjective reaction and good technical and business judgment are the most important tools in making decisions about projects, weighting can be problematic. It is not always possible to describe and assign weight to some of the softer, fuzzier reasons that a project might be important. A product development organization that applies weighting to yield a score that is supposed to reflect the priority/desirability/value/urgency of a project will inevitably find itself at times at odds with the score and rank of a project and what the organization intuitively knows is the real importance of, or danger of, a project. This, then, generally leads to going back to redo the numbers, modifying the objective score of a project so that it more closely reflects what the company plans to do with it anyway.

Occasionally too, a product development organization will find itself in the grasp of immediate management so slavishly enamored of strict adherence to a process that judgment and intuitiveness are subjugated to the absolute output of that process. Important opportunities are likely to be passed up or dismissed in favor of higher-scoring but less worthy endeavors. This is especially likely in portfolio assessment if weighting is used.

By the way, beware of becoming one of those individuals to whom a process is an end unto itself. A process should be a servant, not a master.

A very common and very dangerous tendency is for an organization to include too many projects in its development portfolio, most often in a misguided attempt to please or impress management. One way to avoid the problem is to attain management buy-in and understanding of product development planning and of the stages and requirements of the product development process.

It's easy to understand why the company president bristles when informed by the product development organization that what appears at first blush to be a simple and straightforward project to develop a new product will require three times the resources and five times the time to get to launch than he or she thinks it should. There are always a plethora

of examples that the president can give of other companies that can launch products in a fraction of the time. In reality, the other company's new products might not really be that similar in terms of, for example, clinical and regulatory requirements. But the cause of underproductivity in a product development organization can often be traced to lack of understanding of product development—within management ranks and within the product development group itself. It is clear that if the product development organization understands and engages in the practices of a sound product development planning system, it will be better equipped to educate management. If management, in turn, grasps the basic concepts and is willing to be educated as to which elements of development are absolute quality and regulatory requirements and which elements can not be considered optional, management support is much more likely.

Having too many projects in relation to available resources with the proper and necessary skills means that development work will be impaired and unfocused. Efforts will become disjointed and disorganized as people rush from project to project, putting out fires on some while losing momentum on others. Portfolio management offers the opportunity to apply some of the principles of Henry David Thoreau in the workplace. No, not civil disobedience—although that can sometimes be the net result of failure to institute the relevant principle, which is, of course, *simplification*. If portfolio assessment reveals that there are more projects than appropriate people to work on them, actions must be triggered, or else the exercise of portfolio assessment should be discontinued. If the discipline to simplify and to kill projects is lacking, the portfolio will just keep filling up with more and more projects—all of which seem valuable and desirable. Everyone's time will be spent analyzing projects, filling out data forms, constructing maps, and justifying the necessity of including all of these projects for the success of the company. Financial resources will be drained by trying to support or breathe life into projects that no longer merit investment. Eventually, nothing at all will actually get developed.

KILLING A PROJECT

Don't be afraid to kill a project. If the criteria for killing a project are well thought-out and accepted by everyone involved in the portfolio assessment activity (or at least by a sound majority), the decision to kill a project is overwhelmingly likely to be the right decision.

It can be extremely difficult to pull the plug on a development project. There is a tendency to regard this action as an admission of personal or

- The market opportunity no longer exists.
- A change in business strategy results in poor fit.
- The regulatory environment becomes very unfavorable.
- Raw materials are no longer readily available.
- Required technological capabilities are unattainable.
- Milestones can not be met.
- The entire team agrees that the project is hopeless.

Figure 15.6 Signs that a project should be killed.

group inadequacy or defeat. Sometimes, individuals become so emotionally attached to a project that letting go causes psychological distress. At times, it seems more palatable to kill the project manager than to kill the project. Occasionally, though, people involved with a project that is just not working out will become demoralized, recognizing that the project is hopeless but uncertain of how to convey the agony to decision makers. For them, killing the project would bring a sense of relief and an end to pain.

As shown in Figure 15.6, discontinuing a project should be seriously considered if the criteria for selecting the project no longer apply to a project; if troubling and significant but unforeseen changes in the competitive, regulatory, or medical environment occur; if access to or availability of raw materials becomes seriously compromised; if milestones have not been met and can not be met in the future; or if common sense and good judgment just cry out that the project is hopeless.

Some healthcare companies hold celebratory parties when a project is killed, and others stage mock funerals. Unless an overwhelmingly compelling reason exists—for example, you still have three years development time ahead of you on the project, but yesterday three competitors announced the launch of new products that do the same thing better, more safely, and more economically than your planned product—rather than bury the project, put the idea in the back of the closet. Every now and then, take it out, shake it out, dust it off, and reexamine it. Shifts in company mission, vision, customer needs, market, or technologies might provide an opportunity to resurrect the project in a new environment that would enhance its success.

Portfolio management is a method of making sure that product development activities will support business objectives. The proper mix of development projects will provide a steady stream of new product introductions and assure that the products being developed are the right products.

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16

Components of Product Development Planning

Technology Assessment

Fooling around with alternating currents is just a waste of time. Nobody will use it, ever. It's too dangerous.

—Thomas Alva Edison

In a number of the preceding chapters, the concept of technology assessment has been mentioned. Technology assessment is one of the key elements in the integrated approach to product development encompassed in product development planning (see Figure 16.1). The objective of technology assessment is to identify available technologies that have the

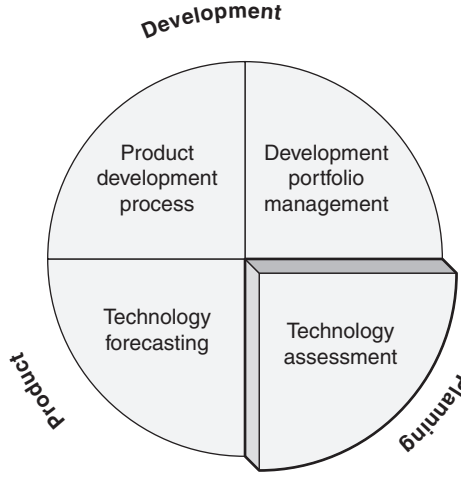

Figure 16.1 Technology assessment is an integral component of product development planning.

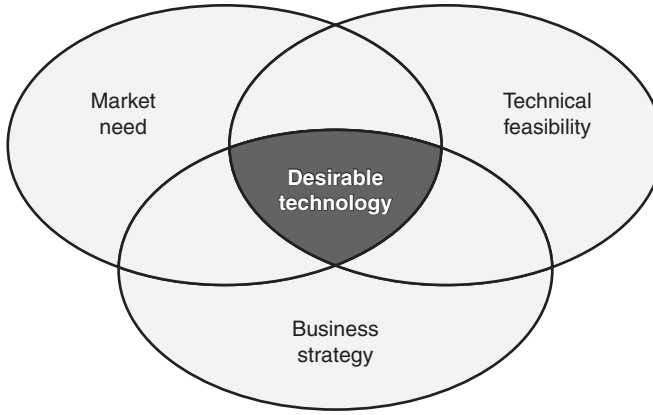

Figure 16.2 Considerations in technology assessment.

greatest fit with the business strategy and market need, as well as a high probability of technical success (see Figure 16.2).

Product development planning allows the formation of a technology strategy by linking an ongoing assessment of existing, new, emerging, and embryonic technologies with the process of technology forecasting as a vision of the future. The technology strategy, in turn, forms the foundation for a portfolio of new potential product development projects. Management of the development portfolio depends on successful implementation of a defined product development process.

Technology assessment means identifying and evaluating existing, new, emerging, and embryonic technologies. It incorporates critical factors—scientific, clinical, regulatory, legal, market-related, social, political, and ethical—that can influence the success, profitability, and life cycle of a technology. Technology assessment has its most pronounced influence on the near- to mid-term planning for new product development.

Healthcare product development requires information from the market to be meshed with scientific opportunities in order to yield a viable, desirable new product. The scientific opportunities may exist or be presented in a plethora of forms, including:

- Basic technological offerings from start-up companies
- University-based applied research programs
- Patents and scientific literature
- New product ideas being developed by other companies

- Product suggestions from customers
- New products already developed, but not yet commercialized
- Marketing and licensing opportunities
- Acquisition targets

These opportunities often enter an organization through research or product development groups, through marketing, or through the business development department of a company. Business development groups may constitute the most common contact from outside companies with an idea, technology, or product to sell.

One typical scenario is for someone from business development at a small company to contact someone in business development at another, larger company. The small company has a technology about which it wants to make a presentation, in hopes of enticing the larger company to provide financial support to continue development work. In exchange, the smaller company will try to negotiate an agreement allowing certain rights related to any future product sales to the larger company. The business development people from the two companies make arrangements to meet to review the idea. From this point on, things all too frequently begin to go astray. For example, while the company with the idea to sell may have a scientific person provide a simplified technical overview, the audience often consists of nonscientist business development personnel and perhaps assorted financial or operations individuals. The audience takes on good faith the always outstanding safety and performance information presented by the company with the idea. Since the audience members are unable or unprepared to ask any relevant and probing questions related to scientific data or regulatory issues, serious potential problems will be overlooked at the onset. Furthermore, since the company receiving the information has no one present with the appropriate grasp of the market or with the relevant and probing questions related to the marketplace or to users, the need or utility of the technology or resulting product will not be confirmed at the onset.

It is clear that the decision-making process with regard to action on the idea will be compromised in this case. If they are too gullible, the decision makers may make a financial commitment to developing a new product for which there is inadequate market need or that has virtually no probability of gaining regulatory approval or clearance. If they are too cynical, the decision makers may believe that the potential is unrealistically overinflated and overhyped and pass up a real gem.

There are other common versions of this scenario, many of which are flawed because the people with the appropriate skills and knowledge bases are excluded from such meetings. Marketing personnel may be present, but

product development personnel absent; or the converse might be the case. The point is that when all of the necessary knowledge is not available to business development efforts that involve assessing existing, new, emerging, or embryonic technology, time, money, and effort are wasted. Perhaps worse, really good opportunities may be lost. Some of the critical skills that come into play in informed technology assessment efforts are given in Figure 16.3. When healthcare products are involved, it makes a great deal

Marketing

- Knowledge of targeted market
- Understanding of targeted customers and users
- Understanding of promotional opportunities and limitations
- Access to information regarding market size, number of procedures, and so on, to establish need
- Familiarity with existing alternatives and competitors, if any
- Cost, pricing, coverage, and reimbursement issues

Scientific

- Ability to assess significance of medical need
- Understanding completeness and validity of safety data
- Understanding completeness and validity of preclinical efficacy studies
- Ability to evaluate any completed or ongoing clinical studies
- Ability to recognize technical "red flags"
- Grasp of feasibility of successful development
- Knowledge of current scientific, health, and medical issues
- Access to IP evaluation resources

Regulatory

- Ability to determine probable required regulatory pathway
- Knowledge of current relevant regulatory issues
- Understanding of testing and manufacturing requirements
- Access to product- or technology-related regulatory history
- Grasp of registration and review time requirements
- Grasp of probability of regulatory success
- Experience in communicating/negotiating with FDA

Figure 16.3 Examples of critical skills and knowledge base for informed technology assessment.

of sense to have scientifically trained, dedicated staff members involved in technology assessment.

When assessing the value of new technological opportunities, it is critical to clarify the customer and the end user, and the magnitude and nature of the clinical need that is expected to be addressed. If there are other technologies in place for use in the same or similar medical conditions, some clear advantages *that will be important to customers* must exist. If there are, for example, presumed advantages in terms of safety, clinical effectiveness, usability, outcomes, or cost, it is important to establish that the differences are qualitatively and quantitatively sufficient to persuade adoption of the resulting new product. One can not simply assume what customers' reactions would be (much less FDA's). The information must come from the targeted customer. Don't forget nondomestic customers. In reflecting on the potential for global new product introductions, any positive or negative cultural issues must be examined.

There may be opportunities for access to a new technology that could replace an existing product that already satisfactorily meets current customer needs. The new technology may be attractive because it offers certain advantages to the manufacturer—perhaps in terms of cost, availability of materials, or greater manufacturing control. In such cases, unless the product changes are completely invisible to the customer, it is once again critical to talk to and listen to the customer before switching to the new technology. There have been countless market failures in the healthcare field resulting from companies neglecting to obtain customer reactions to product concepts or product prototypes before introducing the product.

New technologies can bring added future value to a company if they have the potential of serving as a platform for the future development of a variety of new product derivatives. If an opportunity can become a new company core technology, the life span—and hence the overall value—of the technology can be increased. Similarly, if a licensing agreement to a patented technology is the opportunity being pursued, guaranteed exclusivity along with the proprietary nature of the product technology can serve as formidable barriers to competitive product entries.

Technology readiness and novelty are important considerations. Depending on the scale of development of the technology—benchtop, breadboard prototype, pilot, in clinical evaluation, fully manufactured—different questions about manufacturability limitations or scale-up problems will become relevant. Novelty and readiness, in conjunction with competitive development activities, can influence the likelihood of premature obsolescence because of other new or emerging technologies. When implementing product development planning, it is crucial to integrate the key requirements pertaining to business strategy, customers, and product

Table 16.1 Framework for basic assessment of ideas, projects, and future opportunities.

Issue	**Status**	
Customer/market need	Now met	Unmet
Market opportunity	Small	Large
Market growth	Low	High
Fit with business strategy	Poor	Good
Profitability	Low	High
Profit impact on company	Small	Large
Competition	Strong	Weak
Patent position/exclusivity	Weak	Strong
Time to commercialize	Long	Short
Company technological capability	New	Existing
Regulatory obstacles	Difficult	Less difficult
Investment required	High	Low

attributes into the processes of product development, portfolio analysis, and technology assessment. If the lists of example questions given in this book for each of these components seem redundant, it is because they are purposefully redundant. Identifying the most important considerations, phrasing questions that will give information about those considerations, and consistently analyzing and interpreting that information will ensure proper focus and alignment of product development planning with business objectives. Core issues must be addressed in all key components of product development planning, yet each component will bring in its own new interests and objectives. In keeping with the goal of a unified framework for assessment of new ideas, projects, products, and opportunities, Table 16.1 presents the basic scheme for evaluation, and Figure 16.4 gives some additional topics for questions that might typically be relevant to healthcare technology assessment.

- Developmental stage
- Existing regulatory approval/clearance
- Fit with mid- to long-term business strategy
- Management support
- Outcomes advantages
- Other competitive advantages
- Business risk
- Technical feasibility
- Readiness of technology
- Knowledge of/access to customers
- Positive medical, social, cultural, legal, or ethical issues
- Negative medical, social, cultural, legal, or ethical issues
- Availability of required resources
- Return on investment
- Gross profit
- Potential as platform technology
- Global applicability
- Technology life span/vulnerability to obsolescence

Figure 16.4 Additional issues relevant to technology assessment.

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17

Components of Product Development Planning

Technology Forecasting

Prediction is very difficult, especially about the future.

—Attributed to Niels Bohr

It may seem an elusive goal in these somewhat chaotic and unpredictable times, but technology forecasting is about anticipating the future. Anticipating the future allows the formation of a suitable and planned technology strategy. It also alerts a business organization to the possible need for a shift or an evolution in its business strategy. Be assured, a company involved in medical products that is not involved in technology forecasting will eventually lose its competitive edge. As an integral component of product development planning, technology forecasting is essential to the survival and growth of healthcare companies in an ever-changing environment (see Figure 17.1). The linkage of technology forecasting with technology assessment allows a technology strategy to be defined. The technology strategy, in turn, forms the foundation for filling the product development funnel, and hence the development portfolio, with new project opportunities.

You will notice that the operative word with regard to the future is *anticipating*, not *predicting.* In trying to visualize the course of scientific and technological advances, it is not possible to consider four key elements that would actually allow an informed prediction to be made: (1) serendipity, (2) the quirkiness and unpredictability of Mother Nature, (3) the destructive capabilities of the human race, and (4) the rate of scientific and technological discoveries and advances—even of those that we're quite certain are on the horizon. Consider the following:

- It took 122 years to issue the first one million U.S. patents, twenty-four years to issue the second million, and eight years to issue the one million patents spanning the fifth and sixth million.

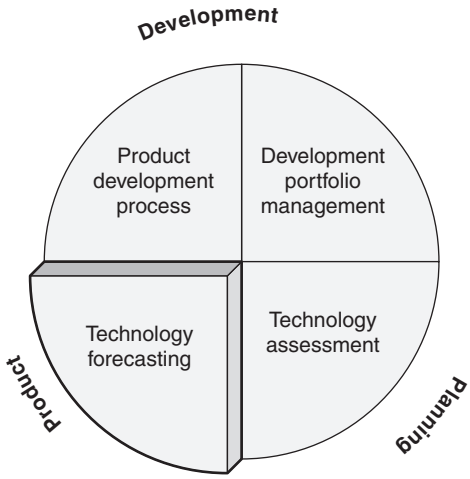

Figure 17.1 Technology forecasting is an integral component of product development planning.

- It took centuries to identify the cause of cholera, two years to identify the cause of AIDS, and about two weeks to identify the cause of severe acute respiratory syndrome (SARS).

For this reason, technology forecasting, which is generally directed at scenarios more than five years in the future, should not strive for precision in terms of events or timelines.

Technology forecasting requires closer attention to pure scientific activity than is required by other elements of product development planning. This is because scientific discovery and technology are interdependent and inextricable (see Figure 17.2). As new scientific phenomena are uncovered, techniques are created to address or approach resulting scientific questions, which results in additional new information and discovery. The new techniques, in turn, can exploit this new information by applying it to other scientific (or medical) needs or problems. This exercise results both in driving further technology development to improve outcomes, and in the revelation of more scientific information through data generation (which leads to more technological advances, and so on, ad infinitum).

As an example, consider the ongoing scientific examination entailed in the human genome project. As the mapping of the human genome proceeds, we have witnessed new opportunities for genetic therapy in which normal, functioning copies of abnormal genes are introduced into the patient to do the work that the abnormal version of the genes is incapable

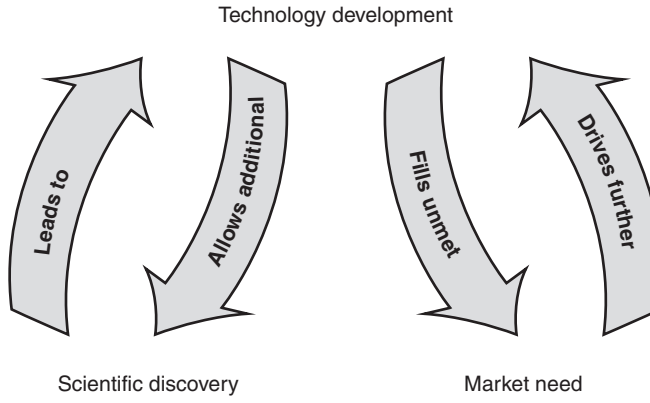

Figure 17.2 The relationship between science, technology, and market.

of doing. We have also been witness to the unpredictable and sometimes disastrous consequences of gene therapy. In just a few years of observation of the likely direction of gene mapping, entrepreneurs have developed or are developing:

- Diagnostic procedures, and the associated chemistries, disposables, hardware, and software
- Therapies to prevent or postpone the onset of symptoms associated with diagnosed genetic predispositions
- Therapies to restore deficiencies resulting from genetic disorders
- Vehicles and devices for the delivery of therapeutic treatments
- Improved (simplified, miniaturized, more rapid) devices and instrumentation to isolate and amplify genetic sequences for therapeutic purposes
- Improved instrumentation and devices for forensic genetic analysis
- Patient-specific courses of treatment based on allelic profiles

Further consideration of each of these items, in turn, can provide more opportunity for speculation and visualization of products in an endless cascade of ideas and applications. Will restorative therapies be conventional drugs? Recombinant enzymes or hormones? Agonists or antagonists of proteins? Antisense molecules? Nucleic acids or cells sourced from the patient? You get the idea.

In imagining the future, a product development organization will require from management an indication of the scope that this visionary process may encompass. To end up with a useful output, there must be some indication of how far and in what direction from the current company mission one can stray in technology forecasting. An open mind is essential in considering the possibilities of scientific and technological advances, while discipline and focus are necessary to stay in sync with the management view of the future company. If there is an absolute, irrevocable proscription against ever becoming a drug company, for example, attention could be given to how the new science might affect diagnostic and surgical procedures, the need for new polymers or other materials, use of disposable or consumable supplies, requirements for specialized instruments and equipment, and so forth. The rapid growth in development and approval of combination products is indicative of some medical product companies' willingness to expand beyond their historically traditional missions.

Like other steps in product development planning, technology forecasting is best served by cross-functional participants. Information for technology forecasting can come from a number of sources, including but not limited to:

- Professional conferences
- Scientific literature
- Patent literature
- Market research
- University alliances
- Customers
- Competitive intelligence networks
- FDA activity and publications
- EPA activity and publications
- National Institutes of Health activity, publications, and clinical trials registries
- Centers for Disease Control and Prevention activity and publications
- Emerging public health issues, both domestic and global

These sources are similar to those from which new product ideas are identified or generated. This is not surprising if you think of technology

forecasting as providing the basis for new product ideas with the more distant future in mind.

While brainstorming and no-holds-barred creativity sessions have their place in technology forecasting, study and extrapolation of trends is very important. Often in the process of technology forecasting, the view is so firmly fixed on the future that the starting point is the present, or possibly even the future. In fact, the starting point for anticipating the future should be the past. An analysis of trends shows how we got to the present and identifies the drivers, obstacles, and success of the outcomes.

There are scientific, technological, political, legal, social, economic, cultural, ethical, and environmental trends that themselves have affected healthcare trends and that have defined the current state of affairs. An understanding of each contributor and an educated, informed extrapolation based on both historical and emerging data will help to maximize the probability of accuracy in the vision of the future. Forecasts that are supported by converging trends will generally be more viable and associated with more significant opportunities. As an example, consider the factors that have been identified as contributing to the emergence of new diseases in humans, such as AIDS, Ebola, SARS, variant CJD (BSE), and 2009 H1N1 influenza virus; to the reemergence of previously controlled diseases, such as tuberculosis; and to the disturbing increase in occurrence of antibiotic-resistant pathogens (see Figure 17.3). By looking back in time, epidemiologists are now better prepared to see ahead and to anticipate the possibility of new diseases arising in certain situations. Technology forecasting in the field of infection control would rely on analysis of the same contributing factors to anticipate the future and to develop new product strategies to deal with the anticipated future.

Sometimes, the voices of scientists—especially those not espousing popular beliefs—are ignored in the process of technology forecasting. The case of duodenal ulcer treatment is an example. For generations, ulcers were managed by dubious dietary therapies and recommendations to avoid stress, then by antacids, and in severe cases by surgery. Then began the era of gastric acid secretion inhibition by histamine H2-receptor antagonists. These drugs became the top-selling pharmaceuticals and are now available over the counter. Another class of antisecretory drugs, the proton pump inhibitors, followed. Not unexpectedly, the indication for surgical intervention for ulcers drastically decreased. In the background, though, was a researcher who doggedly believed that ulcers were caused by bacteria. Though pharmaceutical manufacturers resisted the message, the evidence could not be ignored forever. In 1996, FDA approved the first antibiotic treatment for ulcers.[1] Whether or not the entire evolution from palliative to surgical to suppressive to anti-infective management of duodenal

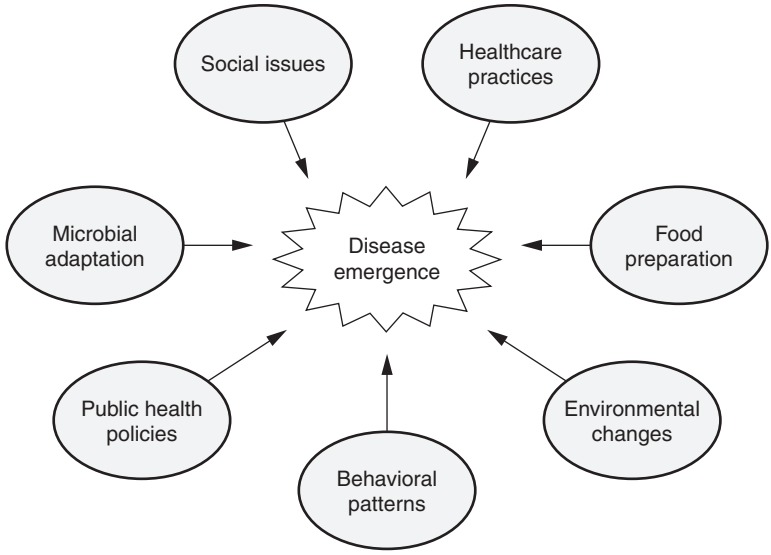

Figure 17.3 Some factors contributing to the emergence of new diseases and the reemergence of previously controlled diseases.

ulcers could have been forecast, the timing of the most recent phase certainly could have been different had greater attention been paid to basic scientific research.

Political agendas can impede the progress of research and the development of new medical products. Whether due to deliberate or self-delusional denial, the failure of certain governments to recognize either the existence or implications of, for example, AIDS, variant CJD, or SARS delayed the quests for diagnostics and therapies.

Analyzing trends and following up with technology strategies based on these analyses can create new sets of problems, or, as product development people prefer to say, opportunities. Since the 1980s, technology forecasting (and resultant product development efforts) have increasingly followed a shift from interest in acute illnesses to addressing needs associated with chronic and long-term conditions. There are a variety of reasons for this emphasis, ranging from lack of glamour and complacency with the adequacy of existing products to the pressures of managed care. Although issues of antibiotic resistance have been recognized for many decades, the development of new antibiotics decreased during the past 20 years, and scant attention has been paid to the R&D of new classes of anti-infective

agents to which microbes could not become resistant. Alternative therapies for a variety of drug-resistant bacterial species are now desperately needed, but the development projects are few and in the early stages. The vigilance, observation, and imagination to spot where trends are going, to differentiate between true trends and fads, and to identify the gaps left in the wake of the trends are part and parcel of technology forecasting. It is an exercise that requires simultaneous analysis of numerous issues of science, research institutions, medicine, marketing, and regulatory affairs, in addition to imagination, knowledge, and understanding of the long-term company business strategy. Figure 17.4 lists some of the topics that might be addressed during technology forecasting.

What do you anticipate/speculate will apply to the following in five years? 10 years? 15 years? 20 years?

- Major challenges in health and medicine
- Vision/mission of the company
- Trends in prevention/diagnosis/treatment/monitoring/cure
- Market potential for these trends
- Compatibility with long-term company vision
- Issues/areas neglected or overlooked if trends are widely pursued
- Opportunities in neglected, overlooked areas
- Targeted customers
- New needs for customers
- Globalization and harmonization of international regulatory and quality requirements
- Technologies that could provide solutions
- Solutions that could be provided by current core/platform technologies
- Availability or sources of enabling technologies
- Groups/institutions working on new relevant technologies
- Healthcare provider/healthcare delivery system restrictions
- Competitors and competitive activity
- Possible regulatory scenarios
- Skills and resource needs to meet the challenges

Figure 17.4 Considerations for technology forecasting.

The areas of government-funded research activities in healthcare, and the priorities articulated by FDA, can foreshadow market need and opportunity. Some of the areas of interest that FDA has expressed are shown in Figure 17.5.

The deliverable at the conclusion of a technology forecasting session should be an identified strategy to monitor some developments and a recommendation to management (with copious justification, of course) to invest and participate in others. All assumptions should be clearly stated in the forecast, and the time horizons should be clear. The nature and degree of participation in follow-up to technology forecasting exercises will depend on the size, vision, and resources of the company. Usually, alternatives for action will include long-range internal research and/or development, codevelopment partnerships with universities or other public or private research groups, and investment in or acquisition of research-oriented companies.

Vaccines and treatments:

- Pandemic influenza
- Antibiotic-resistant TB
- Emerging and reemerging infectious agents
- Bioterrorism agents

Treatments for chemical and radiological weapons agents

Regenerative medicine

Bioengineered tissues and organs

Biomarkers:

- Pharmacogenomics and personalized medicine
- Preclinical and clinical safety indicators
- Surrogate endpoints

Rapid pathogen identification

Predictive disease models

Harnessing bioinformatics

Cell and gene therapy

Pediatric cardiovascular devices

Translation of nanotechnology into devices, diagnostics, and other products

Figure 17.5 Some areas of interest at FDA for the twenty-first century.

Although accurate predictions are what we may fantasize about as we engage in technology forecasting, no one should enter into the process expecting to experience an epiphany. The objective of technology forecasting should not be to predict with assurance events, developments, or timing. Rather, it is to encourage unconventional, creative thinking about new products, unfettered by the constraints and limitations of the present.

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18

Better Double-Check That

A Guide for the Risk-Averse

. . . And more, and more, and more.

—Lewis Carroll

During the various stages of product development, risks and hazards must be identified, analyzed, prioritized, resolved, managed, and predicted. Figure 18.1 shows some of the areas of risk associated with medical product development. The list is not comprehensive, and not all of the issues will be relevant to a particular project or organization. Previous chapters have presented discussions and suggestions related to a number of these risks.

PLANNING FOR PROMOTIONAL OPPORTUNITIES

There are strict regulations regarding advertising and promotion of medical products. When FDA clears or approves a medical device, drug, or biologic for marketing, the agency will define specific indications for use for that product. The indications for use are based on the total package of information provided to FDA, particularly safety and efficacy data. The manufacturer or distributor of the product can advertise and promote the product only for the indicate use(s). It is illegal to promote a medical product for any use other than the FDA-approved indicated uses, that is, it is illegal to engage in off-label promotional activities. Now, FDA does not regulate the practice of medicine, and it is not illegal for a doctor to use a medical product in an off-label indication. There are certain liability risks for the doctor, and for the manufacturer as well, if the doctor chooses to use the product off-label—but it is legal to do so. Have no doubt about this,

Budget management
Changing competitive landscape
Clinical design, including models, endpoints, statistical plan
Clinical failure
FDA
Funding availability, amount, duration
Gamesmanship
Globalization issues
Insufficient human resources
Intellectual property status
Investment in the wrong project
Legal agreements, including licensing and distribution
Management support and involvement
Marketing and promotional limitations
Preclinical failure
Preclinical trial design
Pricing and reimbursement
Product design flaws
Quality and total quality management
Scale-up: time, resources, experience, feasibility
Timing

Figure 18.1 A non-comprehensive alphabetical list of risks.

though—you can not promote the product for off-label use. So, it is important to establish what marketing claims (indications) are mandatory in the view of the company, what indications are desirable, and what development activities will be required to attempt to achieve the articulated corporate promotional goals.

The promotional objectives, of course, have to be realistic given the nature, design, and fundamental intention of the product idea. By the time the clinical plan is being formulated for those products requiring clinical trials, it is essential to have this issue resolved. A good clinical plan asks the right questions in the right manner at the right time. Once the process is rolling, it is very difficult and costly to change the objectives of a clinical

trial to accommodate marketing requests. This applies to nonclinical as well as clinical outcomes evaluations and measurements.

SPEED TO MARKET VERSUS PRODUCT PROMOTIONAL PREFERENCES

A difficult decision may face the product development planning team: is it better to pursue a quicker path to marketing approval by limiting the testing—particularly the clinical testing—to support limited claims, or to delay market entry but be able to launch a product that has been approved for more extensive, valuable indications? The answer will depend on financial resources available to initially bring the product to market, the competitive milieu, anticipated future competition, and sales projections for limited indications compared with projections for broader indications. Bringing a product to market early to establish a market presence and identity, even with curtailed promotional opportunities, has benefits and drawbacks, but should be considered in the planning process.

INTELLECTUAL PROPERTY

Intellectual property (IP) is one of the most important assets of medical products companies. It is the foundation for market dominance and continuing profitability, and is frequently the key objective in mergers and acquisitions. Recognizing the value of an IP portfolio is critical to effective product development planning. There are four major categories of IP: copyrights, trademarks, patents, and trade secrets (see Table 18.1). Consideration of all of these is essential in technology assessment, but patents may be the most germane to product development. Patents confer exclusionary rights to the patent holder. That is, a patent permits the patentee to exclude others from making, selling, or using the patented invention, but a patent does not permit the patentee to do anything with the patent. IP rights are territorial. That is, rights must be sought and granted separately for various parts of the world. Something patentable in the United States may already be proprietary elsewhere, and vice versa.

There would be no pharmaceutical or medical device industries without the benefits of IP. Patents protect early-stage innovation, reducing financial risk and providing encouragement to make the required investments in R&D for innovative therapies, they provide manufacturers who have made the investment to develop a product for FDA approval the opportunity to realize commercial value through exclusivity, and they are integral in the

Table 18.1 Types of intellectual property (IP).

IP	Description
Patent (U.S.)	The grant of a property right to the inventor for a term of 20 years from the date of filing. A patent confers the right to exclude others from making, using, offering for sale, or selling the invention in the United States.
Trademark	A word, name, symbol, or device that is used in trade with goods to indicate the source of the goods and to distinguish them from the goods of others.
Copyright	A form of protection provided to the authors of original works of authorship, both published and unpublished, giving the owner the exclusive right to reproduce or distribute copies of the original work.
Trade secret	Information that is not generally known but that gives the owner a competitive advantage, such as patentable (but unpatented) inventions, manufacturing techniques, business methods, and so on. The owner must take precautions to ensure that this form of IP remains secret since there are no rights conferred to protect the owner from competitors who independently develop or discover the trade secret.

creation of a competitive generic drug market, and its concomitant consumer advantage, following the expiration of the patent rights.

For the purpose of medical product development planning, the strength of an IP portfolio depends on a number of general factors that must be questioned and evaluated: coverage, competitiveness, marketability, territory, licensability, enforceability, and patent life (see Figure 18.2).

IP conflicts occur, with good reason, primarily over medical devices with high market potential, and over the attempt to introduce generic versions of drugs (there are no generic biologics as yet). Large companies are often willing to risk the cost of patent litigation in order to corner a market, even for a limited period of time. When hundreds of millions of dollars (or more) and a decade of time (or more) are invested in developing a new drug, which may have annual sales potential of a billion dollars or more, it is not surprising that the original patentee will go to great lengths to defend the IP against competitors. The term of a new patent is 20 years, but by the time that a typical new drug can be marketed, there are only about 8.5 years of effective life left before its patent runs out. Even with the partial restoration added by the Hatch–Waxman Act (which restores a portion of the patent term that is used up in the clinical and FDA review process), the effective remaining patent life is only about 11 years.[1]

1. *Coverage.* Does the IP position really address and protect the invention in all of its aspects, including product composition, processing steps, intermediate products, and final product?
2. *Competitiveness.* Is the IP really able to exclude competitors from designing around the patent to produce essentially the same product?
3. *Marketability.* Who are the customers that would be interested in the property, and how important is the IP likely to be to them?
4. *Territory.* In what parts of the world does the IP confer exclusivity rights—domestic only, or international?
5. *Licensability.* What is the prospect of licensing the IP to another party, and what value will this bring to the patentee?
6. *Enforceability.* Are the claims defensible, and how will the IP stand up in a court of law—whether the patentee is the challenger or is being challenged?
7. *Patent life.* What is the remaining period of exclusivity offered by the IP? Can patent coverage period be extended through legislative provisions (for example, the Hatch–Waxman Act, which allows restoration of a portion of a patent term to help compensate for time lost during clinical testing and FDA review)?

Figure 18.2 Important factors influencing IP value in medical product development planning.

Conversely, there is a financial incentive to introduce a generic version, to design around existing patents, or to take a chance at willfully infringing an existing patent to get a piece of that same market. Open a national newspaper on any given day, and you'll likely find coverage of a medical product patent dispute.

In September 2011, the America Invents Act was signed into law, marking the first significant change in U.S. patent law since 1952.[2] This act, which the Senate passed in an astounding 89–9 vote, comprises a major overhaul of the nation's patent system, and is meant to ease the way for inventors to bring their products to market, and theoretically to shorten the timeline from idea to product. Bringing the United States into line with most other countries, patents will now be awarded based on whether an applicant was the first to file an idea, rather than the first to invent it. It is hoped that the changes will end the uncertainties that can be caused by disputes over the timing of rival inventions, while also giving limited new rights to challenge weak patents at an early stage.

Unfortunately, globalization has brought about some very dangerous IP nightmares. Some countries are notorious for their absolute disregard for intellectual property laws. Illegally copying proprietary medical products

under different brand names, as well as counterfeiting products and passing them off as original brand-name products is widespread, and has been frequently linked to serious adverse health consequences, including deaths. Globalization has played a major role in this epidemic, in part because of cultural attitudes, absence of quality concerns, economics, open markets, and accessibility to Internet purchases.

DON'T FORGET THE BUDGET

Preparation of a budget for product development stage 2—*feasibility*, is challenging, to say the least. In product development, there is a tendency to overlook things like patent expenses, and to underestimate costs for clinical trials. Obviously, because of their enormous diversity, there is no universal formula that can be applied to the cost of developing a medical product.

Tables 18.2 and 18.3 are intended to be a sobering reminder of elements that may have to appear in the budget that the product development planning team presents to the review committee. Depending on the product, there are provisions for reduced patent and user fees for small companies or for first filings. Despite the misleading name, a user fee is paid by the manufacturer to FDA at the time of a submission for approval or clearance for marketing. It has nothing to do with product users. Some products,

Table 18.2 Some basic costs associated with obtaining a U.S. patent.*

Fee type	Cost ($) 2011–2012
Basic filing fee—utility	380
Utility search fee	620
Patent examination fee	250
Utility issue fee	1740
Patent maintenance fees	
• Due at 3.5 years	1130
• Due at 7.5 years	2850
• Due at 11.5 years	4370
Attorney fees	10,000–50,000

Source: (Government fees) U.S. Patent and Trademark Office; legal fees are estimates.

*Does not include any non-U.S. filings.

Table 18.3 FY 2012 FDA user fees.

Product type	Submission type	Standard fee*
Device	PMA	$ 220,050
Device	510(k)	$ 4,049
Drug or biologic	NDA or BLA **	$1,841,500
	Establishment***	$ 520,100
	Product****	$ 98,970

*Certain conditions may provide eligibility for reduced fees or waivers.

**For applications requiring clinical data.

***Fee is assessed for each prescription drug establishment listed in the approved human drug application as an establishment that manufactures the prescription drug product.

****Fee is applied to each prescription drug and biologic product for which a human drug application has been approved and that may be dispensed only by prescription.

such as orphan drugs, are eligible for relief from user fees. The details and requirements are beyond the scope of this book, but each new product opportunity should be assessed for money-saving options.

CONFLICT RESOLUTION: WHAT ABOUT GAME THEORY?

Being on a team is easy. Maintaining team spirit is not so easy. Sometimes, team members appear to play games to divert attention or resources to self-centered interests rather than to a common goal; and dealing with management seems yet another type of game. The organization clearly does not function as a single organism.

Formally, *game theory* is a branch of mathematics that deals with social situations involving two or more players in which the interests of the players are interconnected or interdependent. It is considered a theory of rational decision making that can be applied in social situations in which each player's outcome or fate depends on what the other players do. In game theory, the term "players" can refer to individuals or groups of any size—teams, companies, armies, governments, and so on. There has been a great deal of interest in developing game theory to be a unifying force that can be applied to all interactions between and among people. Game theory models have been tailored to economics, business, psychology, politics, and

history. Some experts believe that game theory is a crucial tool for understanding the modern business world, and that it has the potential to revolutionize the way people think about business.[3]

Decision-Making Games

In its simplest form, game theory entails what are called zero-sum games and non-zero-sum games, and involves issues of competition, cooperation, and value.

Zero-sum games are situations of absolute conflict. Value is neither created nor destroyed because one player's gain is equal to another player's loss. Zero-sum games are "win/lose" in the extreme. Patent litigation over a generic drug entry can be a zero-sum game. The element of value is market share. If the pioneer company wins, it gets to keep (at least for some period of time) the piece of the market that would have gone to the generic manufacturer, while the generic challenger loses its potential market share. Alternatively, if the generic company prevails, it wins by being allowed to compete by selling the drug, while the pioneer company loses whatever share of the market the generic company will gain.

Non-zero-sum games exist when conflict is less than total, which is the more common condition in business. Outcomes that are favorable, at least to some extent, to all players are obtainable through reaching an acceptable balance of value sharing. This is the classic win/win scenario. No one wins everything, or as much as they'd like to, but everybody gets something. The extent and nature of the compromise determine the outcome, so there is no absolute equilibrium. Each player may place a different value on the prize, and experience a different degree of pain with its sacrifice.

The relevance of the basic principles of game theory to social interactions seems obvious. When competitive players cooperate, they can both gain. When they don't cooperate, it is possible either that one will win and the other lose, or that both will lose. Most game scenarios that will be encountered in the development of medical products will be non-zero-sum games involving multiple players and varying degrees of cooperation and competition.

The big problem with applying game theory tactics to strategic decisions is this: "Underlying the entire structure of game theory is the key assumption that players in a game are *rational*. As game theorists use this term, rationality simply means that a player in an interactive situation will act to bring about the most preferred of the possible outcomes, given the constraint that the other players are also acting in the same way."[4] Right away, you can see the predicament. Even if one excludes those incontestably irrational people one works with, the concept of rationality is relative.

What would constitute preferred outcomes in a given situation is relative. The assumption that there is absolute agreement on the establishment of either rationality or what constitutes preferred outcomes completely ignores human factors, and of all people, those involved in medical product development planning know that you can't do that.

Global Games

Globalization has brought greater access to valuable ideas, practices, technologies, and opportunities. Yet, despite the unifying accomplishments of globalization, cultural differences remain an influential determinant in international economic and business relations. Because of globalization, the determinants of rationality, of value, and of preferred outcomes can be quite varied. One only has to reflect on the discord that has been encountered in the establishment of the European Union to see substantial disparity in the concept of value: who should or should not be members, who did or did not want to be members, acceptance of the unified currency, resource allocation. Yet in the framework of the entire world, Europe is a rather homogeneous place.

In a cultural context, some players may be averse to debate, and therefore appear cryptic or ambivalent in discussions and negotiations. The preference of outcomes may diverge among players because of cultural differences in the importance of individualism versus collectivism. Participation, strategy, and decision-making processes may be tied to cultural predilections toward showing emotion, willingness to wait for resolution, risk aversion, even attitudes toward the other players, for example, degree of deference toward authority, hostility toward specific ethnic or cultural groups, or opinions about women in business. All of these disparate behaviors and opinions can and do, of course, exist also among individuals in what could be considered culturally homogeneous groups. Globalization has simply provided the opportunity for more visibility and greater exposure to such diversity. There exists a need to be sensitive to different viewpoints while maintaining the focus and goals of the team.

Product Development Ecosystem Games

The application of the term "ecosystem" to social systems as well as natural systems is well established and accepted. In all cases, an ecosystem comprises the complex set of relationships between all interacting individuals and environments. FDA has likened the medical product development process to an ecosystem, stating:

> Translating a new idea from a discovery into a medical product is a complex process involving an entire ecosystem consisting of academia, industry, small businesses, payors, physicians, government agencies, and patient and consumer groups. Each member of the ecosystem has an important role to play in bringing a new medical product to market, and each piece of the ecosystem is currently under stress, putting America at risk of losing its competitive edge as the leader in scientific innovation. . . . There is a continuum of concerns that impact the environment for medical product innovation, including intellectual property and patent policies, economic policies, biomedical research and medical technology investments, regulatory reform, and reimbursement policies.[5]

Game theory is often employed as an approach to describe and predict the competing and cooperative members of any ecosystem, natural or social. It can be used as a tool to identify and resolve conflict, and to provide optimal solutions for attaining a beneficial result. Game theory techniques presumably would be applicable to translational programs to advance projects through the product development pipeline.

The lesson, though, is that anyone involved in medical product development can safely anticipate that situational conflict will also exist at some level and, to some degree, between the product development planning team and the FDA. Conflict, cooperation, and compromise with the people who make and enforce the rules of the game present a unique set of issues that affect rationality and the mutuality of preferred outcomes. This is not intended to scoff at game theory, but rather to caution against personalization of the determinants. It is as important to understand your friend as it is to understand your foe. But in our shrinking and often chaotic world, it's becoming more difficult to imagine switching places with any other player in the game.

QUALITY CHALLENGES

At the soul of total quality management (TQM) lies the refusal to accept business as usual. The application of quality principles to all company endeavors—including new product development—strives to make tomorrow's activities more effective and productive than today's. Product development planning should be thought of as applying TQM principles to new healthcare products.

There are some aspects of TQM that make its application to medical product development organizations more challenging than its application

to other areas, such as manufacturing. In fact, research groups and development groups are among the most notoriously resistant to quality management programs. Ask anyone who is both basically knowledgeable of TQM and intimately involved in product development, especially any scientist, and reasons why TQM can't work in product development will easily spring to his or her mind. This rationalization is usually based on the following arguments.

The incremental focus of TQM is incompatible with the saltatory nature of scientific discoveries and advances. It is generally accepted that scientific change is not the steady, incremental acquisition of knowledge. Rather, it is characterized by relatively static periods during which progress revolves around solving problems within the context of what is known and accepted as dogma, punctuated by explosive revolutions that completely change the way we view the world. Therefore, it makes no sense to force-fit inventive technical efforts into a paradigm of incremental improvement.

Monitoring tactics and measurement systems stifle creativity. In product development, adherence to certain processes (such as test protocols and documentation requirements) is mandatory, but there may be resistance to process overload when the driving factor seems to be philosophic or social rather than scientific or regulatory. Creative individuals often bridle and dig in their heels when they are told that they must oblige yet another set of requirements involving process, charts, checklists, and measurements. This leads to locking horns with those individuals who are inflexibly driven, perhaps controlled, by process, charts, checklists, and measurements.

Speaking of measurements, there are obvious difficulties associated with applying quality metrics to creative endeavors. Quality measurements typically associated with TQM are—because they were originally manufacturing-based—difficult to apply to product development. For example, a defect rate per million units manufactured can not be translated into product development efforts. On the other side of the coin, technical people who are used to precision indices, such as pH or tensile strength, are also often uncomfortable with soft, subjective, qualitative TQM metrics, such as customer satisfaction.

Management requires buy-in and adherence to TQM principles but does not support those involved in product development in a manner that allows them to succeed at TQM. In some companies, product development scientists are deliberately isolated from customers; other scientists are disinterested in customers and market issues. Meanwhile, marketing associates are often unwilling to understand or assimilate any technical information; regulatory affairs professionals can regard themselves as members of a secret society with knowledge and information that is shared reluctantly; and manufacturing people may not want to be bothered until they have

a defined product to make. Few, if any, of the product development team members have been prepared to grasp the big picture of customer requirements, market need, competitive environment, technical limitations, quality issues, manufacturability, or regulatory constraints.

Acknowledging these issues as obstacles to TQM fundamentally negates the underlying principle of not being satisfied with business as usual. It implies a rigidity in the practice of TQM that is, in itself, incompatible with the TQM philosophy. Implying that TQM comprises specific defined programs and metrics systems that must be applied to all aspects of a business is fallacious, and this attitude does not befit quality management.

Therefore, it is likely to be necessary to effect a cultural change in order to integrate an understanding of quality processes into healthcare product development organizations. Quality procedures and standards that apply to significant but specific healthcare product development planning activities have already been discussed. They include:

- GLPs
- GCPs
- Design controls

Viewing product development planning as a TQM program, which includes the quality practices inherent in GLPs, GCPs, and—in the case of medical devices—design controls, will facilitate acceptance of a TQM philosophy and recognition of the applicability of TQM to product development.

It is important to always remember that quality is all about customer satisfaction and that the concept of quality encompasses the finished product and all supporting services. The healthcare product development process component of product development planning includes such important post-launch and support activities.

Quality can be defined as conformance to agreed-on customer requirements. Customers may be external customers—such as the end users of a product—or internal customers. To attain quality, a product development organization must therefore know both its internal and external customers, understand its customers' needs, and share a commitment to satisfying customer needs. One must think in terms of an infinite continuum; quality is what the customer wants, and what the customer wants is quality (see Figure 18.3). How a product development organization achieves its quality management goals depends a great deal on the nature of the products being developed and the corporate environment in which the organization must work. For example, a good way for a medical device product development organization to kick off its quality management process initiative would be through attention to elements of design controls. Focus on the customer

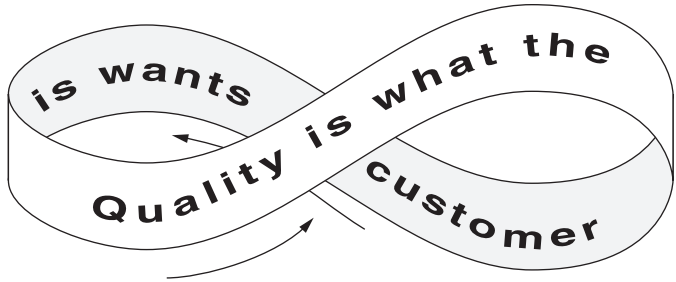

Figure 18.3 The customer/quality continuum.

via human factors analyses and customer needs assessment will simultaneously fulfill an FDA requirement, shorten development time, and define the expectations of the end-use customer. Failure mode analyses will allow anticipation of potential design deficiencies so that the final product design will satisfy the customer.

There is a compelling need to divorce the product development organization from the notion that quality is something attained through the process of inspection and the removal of defective product. Rather than assuming that problems can be fixed ex post facto, those involved in healthcare product development must be committed to preventing problems. There are no universal, standardized methods or solutions for achieving quality. Every product development organization must find its own way, regularly reevaluating quality strategies with an eye set on customer satisfaction and continuous improvement.

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19

Where Do We Go From Here?

We are all pilgrims on the same journey—but some pilgrims have better road maps.

—Nelson DeMille

Witty people have summarized the new product development process in six phases.[1]

Phase 1: Euphoria. Everything looks good—the market potential is enormous and the profits unlimited. Management sees all of the positives. The project is a definite "go."

Phase 2: Disenchantment. A few glitches are identified; problems begin to occur. The market might not be quite as big as first thought, and there could be a few issues with safety, efficacy, or manufacturability. The project is a bit more complex than was originally thought. Management does not like disenchantment, so it adheres to its stand on euphoria.

Phase 3: Chaos. Everyone tries to support management, because everyone knows what happens to negative people and to bearers of bad news. Frantic efforts are made to keep things looking good in the face of contrary evidence. Management is convinced that an incompetent product development team is the reason that euphoria is slipping away. Outside experts and consultants are brought in to analyze and correct the situation.

Phase 4: Search for the guilty. Someone obviously has to be blamed for the problem, but the mess is complex. Who is responsible?

Phase 5: Punishment of the innocent. The selection is made of those who will fall upon the sword. There is no one to defend those who are sacrificed.

Phase 6: Promotion of the uninvolved. Nonparticipants are rewarded. They must have had considerable insight and intelligence to stay away from the project in the first place.

Sadly, it is the truth that we recognize in these words that makes them humorous. For example, following an *annus horribilis* plagued by crippling recalls, FDA sanctions, and sales hits, the board of directors of one of the world's largest medical product companies publicly placed their blame squarely on middle management, and denied that there had been any red flags or systemic failures that had been overlooked by top management. The purpose of product development planning is to help ensure that in the development of new medical care products, neither the projects nor those working on them will be subjected to the futility of the six phases described above.

IN CLOSING

There are a number of points that should be made but that do not fit neatly into any of the preceding chapters. There are also a number of points that have already been made, but that warrant additional emphasis. So, the closing paragraphs of this book offer some exhortations and admonitions.

As members of product development teams interact, there is sometimes conflict caused by traditional and dogmatic views of the relative importance of the models of innovation known as *market pull* and *technology push*. Market pull ideas are those generated by the marketplace because of unmet customer needs; the search is for technology solutions to meet the identified needs. Technology push ideas are generated from the drive to exploit an existing technology by finding additional uses for it; the search is for market needs that can be met by the technology platform. Turf battles between marketing and technical team members over which function takes precedence can impede idea generation and evaluation.

In healthcare product development, market pull and technology push models should not exist independently. Most healthcare companies have invested a great deal of time and money in their technologies, and the incentive and economy of applying the technology bases to addressing new or expanded market needs is understandably strong. Conversely, when an important unmet market need exists, the search for and development of new technologies that might prove effective will be of vital importance. Yet,

acquiring that new effective technology in itself will drive the push to find additional market applications for it. In a healthcare product development organization, the innovative process involves linking both courses so that viable options are never overlooked. A flexible and creative company can simultaneously build on its core technologies and respond to both changing market and technological needs. A strategic fusion of market pull and technology push is the answer.

Maintaining healthcare product development momentum in an era of moving regulatory targets and of vague and vacillating political and economic pressures is difficult. Add to this the difficulties resulting from organizational rearrangements and redefinitions, and it's a wonder that new products are developed at all. Disruptive environmental factors are stressful and counterproductive to development efforts. Defining and adhering to practices consistent with those encompassed in product development planning will facilitate continuity and progress throughout management changes and presidential administrations.

Product development is a path that turns an idea into something that is useful and valuable to customers and that is profitable for the company. Embracing the principles of product development planning will make the journey down the path to new healthcare products safer, faster, and more enjoyable.

A few closing thoughts before we end:

- Focus on the principles of a translational approach.
- Think in terms of looking for solutions, not just for products.
- Haste is not equivalent to speed.
- Don't become a slave to process. Processes should be tools, not drivers.
- Act on the plans that result from the exercises involved in product development planning. If you're just going to put them into a binder for distribution and then forget about them, everyone's time will have been wasted.
- Listen to the voice of the customer.
- Put quality and the well-being of patients above all else.
- View product development planning as applying TQM principles to new product development.
- Work together, challenge yourselves, and go forth and develop new medical products!

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Appendix
Resources

ORGANIZATIONS

AAMI (Association for the Advancement of Medical Instrumentation)
4301 North Fairfax Drive, Suite 301, Arlington, VA 22203-1633
(703) 525-4890
www.aami.org

AAMI is a unique alliance of more than 6000 members from around the world united by one mission—to increase the understanding and beneficial use of medical instrumentation through effective standards, educational programs, and publications. AAMI is the primary source of consensus and timely information on medical instrumentation and technology.

ACRP (Association of Clinical Research Professionals)
500 Montgomery Street, Suite 800, Alexandria, VA 22314
(703) 254-8100
www.acrpnet.org

ACRP is the primary resource for clinical research professionals in the pharmaceutical, biotechnology, and medical device industries, as well as those in hospitals, academic medical centers, and physician office settings.

AdvaMed (Advanced Medical Technology Association)
701 Pennsylvania Ave, NW, Suite 800, Washington, D.C. 20004-2654
(202) 783-8700
www.advamed.org

AdvaMed's member companies produce the medical devices, diagnostic products, and health information systems that are transforming health-care through earlier disease detection, less invasive procedures, and more

effective treatments. AdvaMed members produce nearly 90 percent of the healthcare technology purchased annually in the United States and more than 50 percent purchased annually around the world.

ASQ (American Society for Quality)
600 North Plankinton Avenue, Milwaukee, WI 53203
(800) 248-1946 or (414) 272-8575
www.asq.org

ASQ is a global community of experts and the leading authority on quality in all fields, organizations, and industries. ASQ advances professional development, credentials, knowledge and information services, membership community, and advocacy on behalf of its more than 85,000 members worldwide.

BIO (Biotechnology Industry Organization)
1201 Maryland Avenue, SW, Suite 900, Washington, D.C. 20024
(202) 962-9200
www.bio.org

BIO is the world's largest biotechnology organization, providing advocacy, business development, and communications services for more than 1100 members worldwide. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

C-Path (Critical Path Institute)
1730 E. River Rd., Suite 200, Tucson, AZ 85718
(520) 547-3440
www.c-path.org

C-Path is an independent organization working with scientists from academia, biotechnology companies, the government, and pharmaceutical industry to facilitate applied research, training, and education for enhancing safe and efficacious medical product development.

EMEA (European Medicines Agency; also known as EMA)
7 Westferry Circus, Canary Wharf, London E14 4HB
Tel +44 (0)20 7418 8400
www.ema.europa.eu

The EMEA is a decentralized agency of the European Union (EU), located in London. The Agency is responsible for the scientific evaluation of

medicines developed by pharmaceutical companies for use in the European Union. The outcome of the Agency's evaluation is used by the European Commission to decide whether a medicine can be authorized for marketing in the EU. The company producing a medicine can only market it once the medicine has received a marketing authorization from the European Commission.

FasterCures
1101 New York Avenue, NW, Suite 620, Washington, D.C. 20005
(202) 336-8900
www.fastercures.org

FasterCures works alongside patient advocates, researchers, investors, and policymakers across all sectors of the medical research and development system to stimulate innovative collaborations, increase patient engagement, improve research process and policy, and facilitate greater access and more strategic allocation of capital.

FDLI (Food and Drug Law Institute)
1155 15th Street, NW, Suite 800, Washington, D.C. 20005
(202) 371-1420
www.fdli.org

FDLI is dedicated to providing a leading, innovative, open, balanced marketplace of ideas for education and discourse across the field of global food and drug law that enables key stakeholders to inform, debate, and shape the evolution of public policy and regulation.

GPhA (Generic Pharmaceutical Association)
777 Sixth Street, NW, Suite 510, Washington, D.C. 20001
(202) 249-7100
www.gphaonline.org

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry.

ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICH Secretariat c/o IFPMA 15, Chemin Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland
www.ich.org

ICH brings together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the United States to discuss scientific and technical aspects of drug registration. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.

ISPE (International Society for Pharmaceutical Engineering)
600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609
(813) 960-2105
www.ispe.org

ISPE is the world's largest not-for-profit association dedicated to educating and advancing pharmaceutical manufacturing professionals and their industry.

LES (Licensing Executives Society)
1800 Diagonal Road, Suite 280, Alexandria, VA 22314
703-836-3106
Fax: (703) 836-3107
www.lesusacanada.org

LES is a professional society engaged in the transfer, use, development, and marketing of intellectual property.

MDMA (Medical Device Manufacturers Association)
1333 H Street, NW, Suite 400 West, Washington, DC 20005
(202) 354-7171
www.medicaldevices.org

MDMA represents the interests of innovative and entrepreneurial medical technology companies and provides educational and advocacy assistance to its members.

PDA (Parenteral Drug Association)
Bethesda Towers, 4350 East West Highway, Suite 150, Bethesda, MD 20814
(301) 656-5900
www.pda.org

The Parenteral Drug Association is a leading global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community.

PhRMA (Pharmaceutical Research and Manufacturers of America)
950 F Street, NW, Suite 300, Washington, D.C. 20004
(202) 835-3400
www.phrma.org

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, and its mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by biopharmaceutical research companies.

PQRI (Product Quality Research Institute)
2107 Wilson Blvd., Suite 700, Arlington, VA 22201-3042
(703) 247-4719
www.PQRI.org

PQRI is a consortium of organizations working to generate and share timely, relevant, impactful information that advances drug product quality and development, and to provide a forum to focus critical thinking, conduct research, exchange information, and propose methodology or guidance to pharmaceutical companies, regulators, and standard-setting organizations.

RAPS (Regulatory Affairs Professionals Society)
5635 Fishers Lane, Suite 550, Rockville, Maryland 20852
(301) 770-2920
www.raps.org

RAPS is a global membership organization of regulatory professionals in the rapidly growing medical device, pharmaceutical, and biotechnology sectors, providing education and training, certification, professional standards, research, knowledge-sharing, publications, networking and career development opportunities, and other resources.

GOVERNMENT HEALTH STATISTICS

Agency for Healthcare Research and Quality (AHRQ)
www.ahrq.gov/

AHRQ provides evidence-based information on healthcare outcomes, quality, and cost, use, and access.

Centers for Medicare & Medicaid Services (CMS)
www.cms.gov/home/rsds.asp

The Centers for Medicare & Medicaid Services specializes in statistics, data, and research information. CMS offers to researchers and other healthcare professionals a broad range of quantitative information.

National Center for Health Statistics (NCHS)
www.cdc.gov/nchs

NCHS provides compilations of U.S. statistical information to guide actions and policies to improve the health of the people.

REGULATIONS

Code of Federal Regulations (CFR)
www.gpoaccess.gov/cfr/about.html

Federal Register (FR)
www.federalregister.gov/

Food Drug & Cosmetic Act (FD&C)
www.fda.gov/RegulatoryInformation/Legislation/default.htm

Public Health Service Act (PHS)
www.fda.gov/RegulatoryInformation/Legislation/ucm148717.htm

FOOD AND DRUG ADMINISTRATION

Food and Drug Administration (FDA)
(888) 463-6332
Main web site: www.fda.gov
Alphabetical web site index: www.fda.gov/opacom/hpchoice.html
Index of contact information: www.fda.gov/comments.html

CBER: Manufacturers Assistance Page
www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/default.htm

CDER: Small Business Assistance
www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm

CDRH: Division of Small Manufacturers, International and Consumer Assistance (DSMICA)/Device Advice
www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm

Center for Biologics Evaluation and Research (CBER)
www.fda.gov/BiologicsBloodVaccines/default.htm

Center for Devices and Radiological Health (CDRH)
www.fda.gov/MedicalDevices/default.htm

Center for Drug Evaluation and Research (CDER)
www.fda.gov/Drugs/default.htm

Office of Combination Products (OCP)
www.fda.gov/CombinationProducts/default.htm

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Glossary

Abbreviated New Drug Application (ANDA)—An application for approval of a generic drug.

adaptive clinical trials—Trials designed to allow the use of interim clinical data to modify and improve the study design in a preplanned manner.

biologic—A biological product; a preparation made from living organisms and their products applicable to the prevention, treatment, or cure of diseases or injuries; the category of biologics includes vaccines, blood products, certain diagnostic products, and biotechnology-derived products.

Biologics License Application (BLA)—An application for approval of a new biological product.

biosimilar—A biological product demonstrated to be highly similar to or interchangeable with an FDA-approved biological product.

current good manufacturing practice (cGMP)—See good manufacturing practice (GMP).

clinical trials—The evaluation of a product in studies involving human subjects.

combination products—Complex medical products, such as drug-device, drug-biologic, and device-biologic combinations.

Common Technical Document (CTD)—An international harmonized format for submissions for approval of pharmaceuticals for human use. The CTD does not replace the BLA or NDA, but provides a standardization of the presentation of content.

comparative effectiveness research (CER)—Research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in real-world settings.

design controls—A system to ensure that a new medical device can be used safely and effectively while meeting customer needs; a requirement of current GMPs for medical devices.

development portfolio—The collection of projects available to or being developed by a company.

development portfolio management—One of the four integral components of product development planning; a way to maximize control and minimize risks by keeping a company's strategy for new products compatible with its business objectives.

device—See medical device.

disruptive technology—A new technology that changes things so profoundly that it typically displaces an established technology.

drug—An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and that is intended to affect the structure or function of the body.

failure mode analysis—A determination of malfunction symptoms that appear immediately before or immediately after a failure of a critical parameter in a system or product.

Federal Food, Drug, and Cosmetic (FD&C) Act—The basic law in the United States governing foods, drugs for animals and humans, cosmetics, and medical devices. With its numerous amendments, it is the most extensive law of its kind in the world; also referred to as the "Act."

Food and Drug Administration Modernization Act (FDAMA)—A federal act making numerous changes to the rules governing FDA and industries regulated by FDA.

generic drugs—Approved drugs that are no longer protected by patents and that are approved for marketing by companies without the need for clinical trials; generic drugs are bioequivalent to the original approved drugs.

good clinical practice (GCP)—Regulations and policies governing clinical research.

good manufacturing practice (GMP)—Regulations that establish the minimum requirements for the methods, facilities, and controls used in the manufacturing of medical products.

human factors—The discipline that seeks to analyze and optimize the relationship between human beings and any technology; the interfaces may be physical, perceptual, or cognitive.

intellectual property—Intellectual assets, including patents, copyrights, trademarks, and trade secrets.

Investigational Device Exemption (IDE)—An exemption to the rules prohibiting a medical device that has not been cleared or approved for marketing from being shipped and tested in human subjects.

Investigational New Drug (IND)—An application for permission to test an unapproved drug or biologic in human subjects; an IND provides exemption to rules prohibiting the shipment of unapproved drugs.

managed care—Healthcare provided by a prepaid health plan or covered by an insurance program, in which medical services are reviewed and coordinated to manage access to care, quality of care, and cost of care.

medical device—An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or other condition and that does not depend on chemical action within or on the body and is not dependent on being metabolized to achieve its primary intended purpose.

medical products—Drugs, biologics, and medical devices; these products are regulated by FDA.

new chemical entity (NCE)—*See* new molecular entity.

New Drug Application (NDA)—An application to FDA for approval to market a new drug.

new molecular entity (NME)—An active drug substance that has never been previously approved by FDA.

off-label use—Use of a medical product for an indication not approved or cleared by FDA.

outcomes research—Studies to determine whether use of a technology increases survival, reduces morbidity, improves quality of life, and provides benefits that justify the cost of its use.

pharmacoeconomics—The application of economic principles to the evaluation of pharmaceutical interventions.

portfolio—*See* development portfolio.

preclinical studies—Evaluations of safety and/or efficacy in *in vitro*, *ex vivo*, or *in vivo* systems other than in human beings.

Premarket Approval (PMA) application—An application made to FDA for approval to market certain types of medical devices (Class III) that are considered life-supporting, life-sustaining, or of substantial importance in preventing impairment of human health.

Premarket Notification application [510(k)]—A submission made to FDA to gain clearance for commercial distribution and marketing of certain types of medical devices (Class II and some Class I); clearance may be gained by a finding that the device is substantially equivalent to another Class II or Class I device that is already on the market in the United States.

product development planning—An integrative approach to addressing both long-term and short-term needs and requirements for new products. The four main components are product development process, development portfolio management, technology assessment, and technology forecasting.

product development process—One of the four integral components of product development planning; it describes the stages of healthcare product development (discovery, feasibility, optimization, demonstration, production, and launch and follow-through), as well as the associated tasks, reviews, and deliverables for each stage.

Public Health Service (PHS) Act—A federal act covering a broad spectrum of health concerns, including the regulation of biological products for human use.

quality—What the customer wants; the characteristic of a product or service that meets customer expectations and is free from defects.

Quality System Regulation (QSR)—Medical device GMPs.

recall—The removal or correction, by a firm, of a marketed product because the product is considered to be in violation of laws administered by FDA.

risk assessment—The process of identifying, estimating, and evaluating the nature and severity of risks associated with a product; also called *risk analysis* or *hazard analysis.*

technology assessment—One of the four integral components of product development planning; it is an ongoing identification and evaluation of existing, new, emerging, and embryonic technologies.

technology forecasting—One of the four integral components of product development planning; anticipating the future to allow the formation of a suitable and planned technology strategy.

total quality management (TQM)—The application of quality principles to all company endeavors, with an emphasis on customer satisfaction and continuous improvement.

translational research—Research and development activities geared to turning a scientific idea, discovery, or design into a viable and marketable product.

usability engineering—The application of human factors principles to the design of devices and systems.

user fees—Fees paid to FDA by manufacturers for the review of applications for clearance or approval of new drugs, biologics, and medical devices. The fees provide additional funds to FDA to improve the product review process.

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