CHAPTER

28

Clinical Research from the Industry Perspective

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Clinical trials are conducted to determine whether medicines are safe and efficacious in humans. Pharmaceutical company-sponsored clinical trials are conducted to create a body of research supporting an investigational new medicine prior to submission for approval to the Food and Drug Administration (FDA).

Currently, industry-sponsored clinical trials are being conducted on 2200 medicines in 800 disease conditions worldwide.[1] In the United States alone, approximately 1000 industry-sponsored clinical trials are currently in progress. This research leads to approval of 35–40 new medicines every year. In addition to industry-sponsored clinical trials, approximately 3000 government-sponsored studies at the National Institutes of Health (NIH) and other federal agencies are currently being conducted.[2] In order to fully understand clinical research from the pharmaceutical industry perspective, it is important to define the components of the industry and discuss the challenges under which the components operate.

The major components of the pharmaceutical industry are traditional pharmaceutical companies, stand-alone biotechnology companies, and "biopharmaceutical companies" that represent a melding of traditional and biotechnology approaches to discovery. In addition, there are medical device companies that, again, are either stand-alone entities or folded into larger pharmaceutical companies.

1. COMPONENTS OF THE PHARMACEUTICAL INDUSTRY

1.1. Traditional Pharmaceutical Companies

Traditional pharmaceutical companies have been in existence for more than 100 years. Early in their histories, many produced chemicals. In the years during and immediately following World War II, many companies perfected mass production techniques, and penicillin was produced on a large scale for the war effort. These companies became the large, traditional pharmaceutical companies that discover, develop, manufacture, and market small molecule prescription medicines.

Traditional pharmaceutical companies identify and develop new medicines by large-scale screenings of new chemical entities, which they have patented or licensed from other sources and which they predict will have medicinal activity. Upon identification of a compound exhibiting activity, the compound is submitted to preclinical pharmacology and preclinical safety testing. Compounds that exhibit desirable safety and efficacy profiles then undergo years of clinical testing to determine human safety and efficacy.

Attrition is a major issue in the development of new medicines. Although thousands of potential medicines (both new chemical entities and medicines seeking

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approval which are refinements of previously-approved medications) are screened for medicinal activity, only a few new chemical entities exhibit desirable properties and warrant continued investigation. Indeed, for every 5000 potential new medicines developed, only a handful of new chemical entities survive chemistry and preclinical studies (including animal research and *in vitro* studies), and of those, only 1 or 2 new chemical entities continue through clinical research and become approved for use. The entire process from new chemical entity to approved medicine typically takes between 11 and 15 years. The Tufts Center for the Study of Drug Development, which provides strategic information regarding drug development to drug developers, regulators, and policy makers, depicts the process of developing a new chemical entity from the chemist's bench through preclinical testing and, eventually, through clinical testing and regulatory approval as shown in Figure 28-1.[3]

The Tufts Center also estimates that the cost of bringing a new chemical entity to market is approximately $802 million.[4] This figure is based on its survey of 10 drug companies and includes the following costs:

- Out-of-pocket discovery and preclinical (animal and *in vitro*) development costs
- Out-of-pocket clinical costs
- Attrition rate (the pace at which a compound undergoing clinical trials will fail and be removed from the testing regimen at the various clinical phases)
- Clinical success rate (the probability that a compound undergoing clinical trials will result in an approved medicine)
- Development times and the cost of capital over those periods of time[4]

The FDA has documented the impact of attrition of new drugs (both new chemical entities and product refinements) in clinical research as they progress through their review and approval process, as shown in Table 28-1.[5]

1.2. Biotechnology Companies

The methods used by biotechnology companies to discover new medicines are different from those of traditional pharmaceutical companies. Biotechnology is a collection of technologies that capitalize on the functions of various cell components, including DNA and proteins, within a given type of cell or among different types of cells. Biotechnology tools and techniques are used to study the molecular basis of health

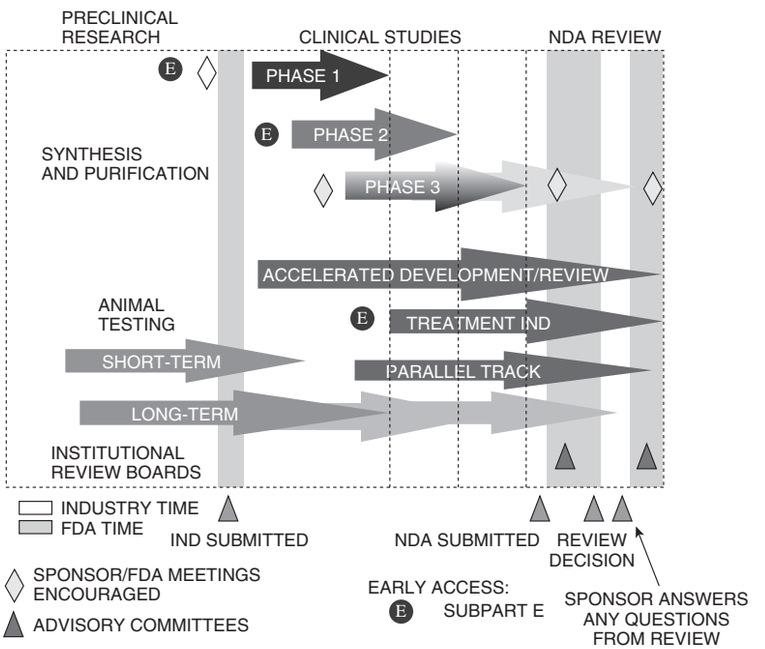

FIGURE 28-1 The new drug development process: Steps from test tube to new drug application review.

TABLE 28-1 FDA Approval Rates for Drug Testing in Humans

	Number of Patients	Length	Purpose	Percent of Drugs Successfully Tested*
Phase 1	20–100	Several months	Mainly safety	70 percent
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety but mainly effectiveness	33 percent
Phase 3	Several hundred to several thousand	1–4 years	Safety, dosage, effectiveness	25–30 percent

• For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 will successfully complete phase 1 trials and go on to phase 2; about 33 of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

• Note: The data presented above include approval of new chemical entities as well as approval of medicines which are refinements of previously-approved medications.

and the changes that take place as a result of disease. This knowledge is resulting in improved and novel methods for treating and preventing disease. By exploiting the extraordinary specificity of cells and biological molecules in their interactions, biotechnology products can often solve specific cellular problems efficiently and with minimal adverse events. By using biotechnology research applications, insights are being gained into the precise details of cell processes, including the following:

- The specific tasks assigned to various cell types
- The mechanics of cell division
- The flow of materials in and out of cells
- The path by which undifferentiated cells become specialized
- The methods cells use to communicate with each other, coordinate their activities, and respond to environmental changes[6]

Biotechnology therapeutics have been approved by the FDA to treat many diseases, including anemia, cystic fibrosis, growth deficiencies, rheumatoid arthritis, hemophilia, hepatitis, genital warts, transplant rejection, and leukemia and other cancers. It is expected that biotechnology will continue to make possible improved versions of today's therapeutic regimes as well as treatments that would not be possible without these new techniques. Currently, there are more than 370 biotechnology vaccines, biologicals, and drug products being investigated in clinical trials, targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, immune suppression, immune stimulation (including AIDS), and arthritis. Biotechnology is also critical in many nontherapeutic areas, including medical diagnostic tests, food science, environmental science, industrial applications, and DNA fingerprinting used for criminal investigations and forensic medicine.[6]

The field of biotechnology has mushroomed since 1992. United States revenues increased from $8 billion in 1992 to $39.2 billion in 2003, and research and development (R&D) costs exceeded $17.0 billion in 2003.

The biotechnology product development and regulatory approval processes are similar to those of traditional drug companies and are shown in Figure 28-2.

The basic tools of biotechnology include

- Recombinant DNA technology—used to manufacture products such as human insulin and hepatitis B vaccine;
- Advanced methods in cell culture;
- Monoclonal antibody technology, which uses immune system cells that make highly specific proteins called antibodies;
- Proteomics—the systematic study of the structure, function, cellular location, expression, and interaction of proteins within and between cells; and
- Genomics and pharmacogenomics—analysis of gene structure, expression, and function to tailor therapeutics to the genetic makeup of individual patients with the goal of identifying genetic differences that predispose patients to adverse reactions to certain drugs or make them good subjects for other drugs.[6]

Current medical uses of recombinant DNA techniques, in conjunction with molecular cloning, include:

- Production of new medicines and safer vaccines;
- Treatment of some genetic diseases;
- Controlling viral diseases; and
- Inhibition of inflammation.

In addition, recombinant DNA technology is important in agriculture and food sciences, environmental sciences, and in developing biodegradable plastics.[6]

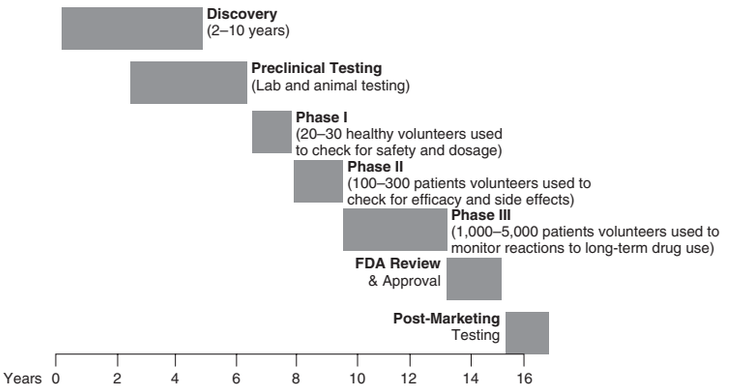

FIGURE 28-2 Overview of the drug discovery process. Reprinted with permission by Ernst and Young (2005).

Improvements in cell culture technology have increased our understanding of the molecular basis of the cell cycle. Scientists have found that the rigorously controlled sequence of steps in the cell cycle depends on both genetic and nutritional factors, and that a delicate balance exists between factors that stimulate cell division and those that inhibit it. Any disruption of this balance leads to uncontrolled cell proliferation (cancer) or cell death (apoptosis).[6]

Current monoclonal antibody research is being conducted to develop methods to selectively suppress the immune system in organ transplantation patients and those with autoimmune diseases. Additionally, a new generation of vaccines is being developed that consists of only the antigen, not the actual microbe. These vaccines are produced by inserting the gene that produces the antigen into a manufacturing cell, such as yeast. During the manufacturing process, each yeast cell makes a perfect copy of itself and the antigen gene. The antigen is then isolated and used as a vaccine without the risk of transmitting the virus.[6]

An ever-expanding knowledge base in proteomics and genomics is serving as the foundation for the following initiatives:

- Predictive tests for diseases that can be prevented with targeted interventions
- Fundamental changes in the way drugs are discovered, tested, and developed
- Therapies that are tailored to the specific genetic makeup of individual patients
- Therapies that address and sometimes correct the biochemical causes of a disease rather than only alleviating the symptoms[6]

For example, gene therapy is a promising technology that uses genes or related molecules such as RNA to block mutated genes and thereby to treat diseases. Research is currently being conducted to determine whether instead of injecting patients with missing proteins to treat deficiencies, patients could be administered nondefective genes to enable the patient's body to produce previously deficient proteins and correct the genetic defects.[6]

Pharmacogenomics is the study of genome-derived data elucidating individual patient genetic variations to predict disease risk and progression and the response by individual patients or groups of patients to specific drugs. Following the 2003 completion of the human genome sequence, the expected impact of genetics and genomics on the diagnosis and treatment of disease seems endless, and it is predicted that pharmacogenomics will be crucial for successful discovery, development, and delivery of new medicines.

In order to study pharmacogenomics, appropriate biomarkers must be identified, and tools to measure biomarkers must be developed. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a drug. Traditional biomarkers have been used to ascertain efficacy and safety of medicines for large populations. One widely used traditional biomarker is the measurement of blood pressure as an indicator of cardiovascular health. For individualized therapy, pharmacogenomic biomarkers are being developed to identify individuals likely to benefit from a particular treatment as well as those individuals at risk from the same treatment.[7]

The economic impact of the use of biotechnology to develop medicines and biologicals is beginning to unfold. It is expected that the use of these techniques to test the safety and efficacy of medicines early in the drug development process will have a positive impact on the total development cost. For example, if, by

using biotechnology techniques, compounds early in the development process are found not to possess expected attributes, work on these compounds can be halted in favor of other compounds with more promising profiles. Improved profitability might also be realized by shortening the product development process as a result of using a single technology at many steps in the process. For example, a small piece of DNA used to locate a gene might eventually become a component of a diagnostic test. Similarly, a monoclonal antibody developed to identify therapeutic leads might be used to recover and purify that therapeutic compound during scale-up.[6]

Biotechnology has already favorably impacted the costs of diagnostics. These diagnostics are not only less expensive than those produced by traditional methods but also more accurate and quicker than previous tests. These changes greatly improve a patient's prognosis by allowing for earlier diagnoses of disease processes.[6]

1.3. Biopharmaceutical Companies

The pharmaceutical industry trade group, Pharmaceutical Research and Manufacturers of America (PhRMA), coined the term *biopharmaceutical* industry.[8] Traditional pharmaceutical companies use this term to describe the incorporation of biotechnology principles. Pharmaceutical companies traditionally discover medicines by studying chemical reactions in the body, specifically searching for the effect on a specific disease target, whereas biotechnology develops methods that capitalize on the attributes of cells and use DNA and proteins to modify the cell functions as a way to combat disease. In recent years, traditional pharmaceutical companies have adopted many of these new technologies either by developing biotechnology groups within their own organizational structures or by partnering or purchasing biotechnology companies. This convergence of biotechnology and traditional pharmaceutics has led to the development of biopharmaceutical companies, which possess strengths from both disciplines.

1.4. Medical Device Companies

The process of developing a medical device is different from that of developing a new medicine, although developing a medical device is time-consuming (up to 15 years) and may be expensive (up to $350 million). Also, although there are three different classes of medical devices from a regulatory standpoint, the development of all classes of medical devices follows a stepwise process as outlined here.[2]

1.4.1. Basic Research

Primary to development of any medical device is the underlying basic research. Basic research—typically conducted by physicists, biologists, and mathematicians—provides the fundamental understanding of physical phenomena (e.g., gravity) and human physiology and the interaction of the two.[2]

1.4.2. Applied Science

Based on the fundamental research, scientists develop a prototype device believed to have a medical application. By using computer simulations with the prototype design, scientists can predict the feasibility of the design as well as projected safety and efficacy. In addition, during this stage, scientists can estimate the costs of "scaling up" the prototype to produce a commercially viable medical device.[2]

1.4.3. Engineering

During the engineering stage, fully operational products designed to meet clinical needs are developed from the prototype. Not only is the medical device developed but also all necessary hardware and software are developed and integrated into the medical device.[2]

The device is then tested in animals to evaluate the reliability of the product. When the device has proved to be reliable, it is then tested in human volunteers to evaluate safety, efficacy, and user acceptance.[2]

1.4.4. Commercialization Stage

The medical device is prepared for final use. Detailed clinical trials and testing are performed to secure final regulatory approval and to support product labeling. Marketing plans are developed to produce necessary training tools and to address pricing issues, and manufacturing capacity is established for commercial product production.[2]

1.4.5. Classification and Regulations Surrounding Medical Devices

There are three classes of medical devices defined by the complexity of the device and the amount of risk they present to the user:

Class I: These devices are not used to support or sustain life but do require general controls. Examples of class I medical devices are surgical gloves and tongue depressors.

Class II: These devices not only require general controls but also must meet performance

standards. An example of a class II medical device is a hypodermic needle.

Class III: These devices sustain or save lives and require premarketing approval, similar to that of a new medicine. Examples of class III medical devices are ventilators, x-ray machines, and vascular stents.[2]

2. ISSUES IMPACTING INDUSTRY CLINICAL RESEARCH

Pharmaceutical company-sponsored clinical trials are conducted to support labeling claims made for a new medicine, biologic, or medical device. These trials are similar to those designed and conducted by any noncommercial entity such as the NIH or an academic medical center; however, there are additional clinical trials that pharmaceutical companies must conduct, either as necessary to support the new medicine in the marketplace or as required by regulatory agencies.

Recent additions to regulations regarding the design and conduct of clinical trials have created new challenges for the pharmaceutical industry. The number of subjects and length of therapy required for a New Drug Application (the dossier of clinical, preclinical, chemistry, and manufacturing information about a medicine seeking approval) has been steadily increasing. In addition, the FDA has required that measurements of safety and efficacy and the biostatistical analyses used to evaluate the clinical trials parameters be increasingly rigorous.

The issues impacting the industry's conduct of clinical research are interrelated. As regulations surrounding the development of new medicines and the clinical trials used to support claims of efficacy and safety become more encompassing, the costs incurred to develop new medicines increase accordingly. Therefore, as costs increase, pressures on the pharmaceutical companies by both the public who use and pay for the medications and their company shareholders impact on the conduct of pharmaceutical business.

2.1. Voluntary Postapproval Trials

Many clinical trials are conducted by pharmaceutical companies after new medicines are approved. Although it might seem that the approval of a new medicine would signal the end of clinical investigations, that is rarely the case. More often, the pharmaceutical companies conduct additional long-term safety and efficacy trials designed to answer questions that did not need to be addressed during phases I–III, including:

- Determination of the medicine's place in the array of medicines already available to treat the condition under study;
- Cost-effectiveness of the medicine;
- The effect of the medicine on patients' quality of life; and
- The safety and efficacy of the medicine on specific subpopulations of patients.

2.1.1. Clinical Outcomes Trials

Large-scale late phase III and phase IV clinical outcomes trials are being conducted with increased frequency by industry. These outcomes trials, which are not FDA mandated but are essential for a fuller understanding of a new medicine, are designed to measure the long-term safety and efficacy of a new medicine on large patient populations. These outcomes trials typically collect morbidity (including myocardial infarction and stroke frequencies) and mortality data from the use of a new medicine by patients for a period of up to five years. These trials are funded by the industry sponsor (usually the pharmaceutical company developing the new medicine under study), but they are typically conducted by independent contract research organizations (CROs). Sponsors engage CROs to conduct any or all trial-related duties and functions. These duties may include selecting study investigators and investigational sites, conducting study-specific training of study site personnel, and monitoring and reconciling study-generated data. Use of CROs is contracted with the understanding that the CRO is acting in lieu of the sponsor, but that the responsibility for the quality and integrity of the study data remains with the sponsor.[9,10]

Data from these trials are typically analyzed by independent data coordinating centers hired by the sponsor to conduct biostatistical analyses, and an additional level of periodic monitoring of study data is typically performed by a data safety monitoring board (DSMB). A DSMB is another entity independent from the sponsor of the trial and is charged with the evaluation of the safety of a study and the determination of whether a study should be continued or terminated based on benefit-to-risk ratio. DSMBs review study protocols and data collection methods, define safety parameters, review adverse events occurring during a clinical trial, and determine whether an interim analysis of a clinical trial is appropriate based on safety and efficacy findings, and if so, conduct the interim analysis. A DSMB may decide to terminate a trial exhibiting an unfavorable safety profile for the new medicine, may terminate a trial if the new medicine exhibits overwhelming benefits over the compara-

tive treatment, or may decide to let the trial continue to its conclusion. DSMBs are composed of clinicians with expertise in relevant safety concerns. DSMBs have ethical responsibilities to the study subjects participating in the trial and scientific responsibilities to the investigators to ascertain that the study's objectives are being met.[9,10]

2.1.2. Product Placement Studies

When the FDA approves a new medicine, the clinical trials on which the approval is based are typically designed to evaluate the new medicine in study patients against placebo (a chemical entity with no medicinal effects) and against the accepted standard medicine prescribed for the condition under study. However, while the investigational medicine undergoes years of clinical testing, it is possible that the FDA will approve another new medicine developed for the same medical condition. Therefore, it is likely that the pharmaceutical company will pursue additional clinical trials after approval to compare the safety and effectiveness of its new medicinal product against other medicines to assure the new product's viability in the marketplace. These product placement studies are typically conducted against the following types of medicines:

- Current market leaders
- Expected future market leaders
- Medicines in the same chemical class
- Medicines in the same therapeutic class

2.1.3. Pharmacoeconomic Trials

Postmarketing clinical trials may also be conducted to ascertain cost-effectiveness of a new medicine. In these studies, costs and consequences of treatment are simultaneously measured to determine whether the benefits of a new medicine justify its costs. These trials may be conducted with the new medicine alone or in comparison with other medicines currently available or other modes of treatment (i.e., hospitalization and/or surgical intervention). The goal of a pharmacoeconomic study is to determine whether the expense incurred by the use of a new medication is justified in comparison with the cost of existing medication as well as potential savings resulting from a decrease in the number of physician visits, emergency room visits, length and number of hospitalizations, ancillary transportation costs, and the number of days of work lost by patients taking the new medication. The results of these pharmacoeconomic studies are analyzed by the large providers of prescription medicines (i.e., national, state, and local governments), health maintenance organizations, and pharmacy benefit management companies to determine the new medicine's place in their formularies (a compilation of medicines for which the providers will pay).[11]

2.1.4. Quality of Life Studies

Other postmarketing studies are conducted to determine the effect(s) of the new medication on patients' quality of life. These trials are designed to measure patients' reactions to a new medicine (including efficacy measures, safety measures, ease of use, convenience, and costs). Data are collected using quality of life questionnaires completed by patients addressing their current lifestyles, past experiences, and expectations for the future. The questionnaires are then assessed to determine whether patients are pleased or displeased with the new medication.[12]

2.1.5. Patient Subpopulation Studies

Other marketing studies are conducted to evaluate a new medicine in specific patient populations (i.e., elderly, pediatric, or immunosuppressed patients) or in patients taking specific concurrent medications that may not have been studied in-depth during the studies conducted for regulatory approval. These trials are designed to evaluate particular issues that might arise in these subpopulations that could not have been ascertained from earlier studies.

2.1.6. Postmarketing Surveillance of Medical Devices

Postmarketing surveillance of medical devices is conducted to evaluate the device in actual use by documenting the following parameters:

- Frequency of ongoing service and preventive maintenance of the devices
- Monitoring of performance
- Frequency of adverse events occurring during use of the device

Based on the postmarketing information, the manufacturer may either provide upgrades for the device or, more likely, develop an improved model based on the experiences of the first model and repeat the regulatory process.[2]

2.1.7. Ethical Considerations

As discussed in Chapter 2, there is an abundance of issues surrounding ethics of clinical trials and protection of human subjects participating in these trials.

One issue that impacts on pharmaceutical company-sponsored clinical trials as well as nonpharmaceutical company-sponsored trials (e.g., those sponsored by NIH, the Centers for Disease Control and Prevention, the World Health Organization, and the Bill and Melinda Gates Foundation) involves the ethical considerations of conducting placebo-controlled clinical trials in areas of socioeconomic depression.[13,14]

Historically, regulatory agencies have favored placebo-controlled studies for proving safety and efficacy of new medicines. Although this method is useful for the initial approval of a new medicine, in the case of long-term, costly therapies (e.g., antiretroviral medication for the treatment of HIV infection), there are often large-scale initiatives to study the new medication in areas where the disease under study has had devastating effects and the area is unable to afford the new medication (e.g., sub-Saharan Africa). The ethical issue in this case is whether placebo-controlled studies are ethically acceptable or whether an active therapy that is less expensive than the new medication (either a different medication or the new medication at a lesser dose and/or duration of therapy) is more appropriate. Proponents of placebo-controlled trials argue that placebo is essentially equivalent to the current "standard of care" in the region—that is, that no therapy is available to patients. They also make a statistical case that the number of patients required to compare an active medication to placebo is less than with an active control, which also leads to reduced costs to conduct the trial. Opponents of placebo-controlled trials state that equivalency studies—those conducted when a particular regimen that has already been proved effective is compared to a second regimen that is about as effective but less toxic or expensive[13]—are more acceptable.

2.2. Regulatory Issues

2.2.1. Biostatistical Analysis

Regulatory requirements for biostatistical analysis of industry-sponsored clinical trials have become increasingly rigorous. Statistical methodology for identifying primary end points and for analyzing all clinical trials data must be defined prior to beginning a clinical trial, and primary end points must exhibit statistical significance at the $p < 0.05$ level. Secondary end points may also be defined, but the FDA will not accept secondary end points alone to support labeling. Furthermore, even if clinical trials show clinical or medical significance, without statistical significance as defined previously, the FDA will not accept clinical or medical significance alone.[9]

2.2.2. Postmarketing Studies

In addition to the postmarketing studies performed voluntarily by the pharmaceutical company, regulatory agencies may also require that additional clinical trials be conducted after regulatory approval. One issue facing regulatory agencies is the dichotomy between the types of patients participating in preapproval clinical trials and those patients who will ultimately use the new medication postapproval. Patients selected for phase II and III clinical trials (phase I subjects are usually healthy normal volunteers) tend to be of young to middle age and relatively disease-free except for the condition under investigation and free of medications other than the investigational drug. By selecting these patients, physicians, biostatisticians, and regulators can evaluate the effects of an investigational drug without the confounding issues of drug–drug interactions and adverse events that might stem from concomitant illnesses rather than the condition being evaluated.

Although this methodology is useful and albeit necessary in evaluating investigational new drugs, it presents formidable issues when the investigational drug is approved for use by the general public. Upon approval, the drug will be used by different types of patients than those used in evaluating the drug for the approval process. In recent years, several medicines, including the following, were withdrawn from the U.S. market as a result of safety issues that were not apparent until the medicines were used by the general public under less stringent conditions than those under which clinical trials were conducted:

- Terfenadine, an antihistamine that exhibited drug interactions causing cardiotoxicity
- Ticrynafen, an antihypertensive medication that caused hepatotoxicity
- Flosequinan, a congestive heart failure medication shown to increase mortality[15]

In addition, rofecoxib (sold under the name Vioxx®), an anti-inflammatory medication, was voluntarily withdrawn from the U.S. market after the DSMB overseeing a long-term study of the drug in gastrointestinal disease recommended the study be halted because of an increased risk of serious cardiovascular events, including myocardial infarction and stroke.[16]

These issues have led the FDA to expand its requirements for postmarketing studies.[17] Postmarketing studies are required by the FDA of pharmaceutical companies not for initial approval of a drug but to provide the regulators additional information. Data from postmarketing studies typically address the following issues:

- Safety and efficacy in a wider patient population than that tested during phases I through III of the drug approval process
- Additional information on prescribing/use of a product
- Drug-interaction data
- Product quality information

The FDA is currently requesting postmarketing studies in 73% of approved new medications,[17] with a steady increase in the median number of patients from 30 in the 1970s to 123 in the 1980s and 920 in 2003.[18]

2.2.3. Patent Issues

2.2.3.1. Medicines and Biologics

A patent gives an inventor the right to be the only entity to manufacture and sell an invention for the life of the patent, typically 20 years. In the case of pharmaceutical companies, the invention is a new chemical entity, a new device, a new process, or a new biological product.

Pharmaceutical companies rely on government-granted patents to protect their huge research and development investments in new medicines they believe will exhibit medicinal efficacy. Without these patents to protect all of the inventions necessary to develop a drug for this period of time, other companies could copy the drugs immediately and offer their versions at prices that do not have to reflect the costs incurred to develop the drugs. This would seriously impact the pharmaceutical companies' abilities to recoup their expenses and reinvest in other research projects. Since the length of time to develop a new chemical entity into an approved medicine typically exceeds 10 years, the number of years remaining to recoup expenses and make a profit is reduced accordingly.[19]

In response to this issue, the FDA has developed a new initiative making it more attractive for pharmaceutical companies to conduct research leading to a second indication in a recently approved medication. Upon approval of the second indication, the FDA can extend a drug patent for an additional three years. This is attractive for the pharmaceutical company since it allows the company to recoup some of its development costs for the new indication prior to the medicine's patent expiration.

2.2.3.2. Medical Devices

Unlike new chemical entities that are patented early in their development, discoveries leading to the development of new medical devices are often not patented. These discoveries occur during the basic research stage of development, and either they are not patentable or the decision is made that the likelihood of requiring an early patent is outweighed by the likelihood that the usable patent life after full development of a device would be restricted. This extends the number of years that a device can be sold with patent protection.[2]

2.3. Financial Pressures

The R&D expenditures in the pharmaceutical and biotechnology industries continue to exceed R&D expenses (as a percentage of annual revenues) in any other area of the U.S. economy. The 2005 *Pharmaceutical Industry Profile* published by PhRMA[9] provides a spending figure for total biopharmaceutical R&D in 2004 of $49.3 billion, which represents approximately 17% of annual revenues. In comparison, the percentage of R&D compared with annual revenues for all U.S. industries in 2004 was 3.9%.

Table 28-2 contrasts published sales and R&D data for several major pharmaceutical companies and biotechnology companies for the years 2003–2005.[20]

TABLE 28-2 Sales and Research & Development Data for Selected Major Pharmaceutical and Biotechnology Companies

	2003			2004			2005		
	Sales	*R&D*	*R&D as % of Sales*	*Sales*	*R&D*	*R&D as % of Sales*	*Sales*	*R&D*	*R&D as % of Sales*
Pfizer	$45.19	$7.13	15.78%	$52.52	$7.68	14.62%	$51.3	$7.4	14.5%
GlaxoSmithKline	$38.27	$4.96	12.96%	$39.22	$5.47	13.95%	$37.3	$5.4	14.5%
Novartis	$24.86	$3.76	15.12%	$28.25	$4.21	14.90%	$32.5	$4.9	14.9%
Merck	$22.49	$3.18	14.14%	$22.94	$4.01	17.48%	$22.0	$3.9	17.5%
Bristol-Myers Squibb	$20.89	$2.28	10.91%	$19.38	$2.50	12.90%	$19.2	$2.8	14.3%
Eli Lilly	$12.58	$2.35	18.68%	$13.86	$2.69	19.41%	$14.7	$3.0	20.7%
Amgen	$8.36	$1.66	19.86%	$10.55	$2.03	19.24%	$12.4	$2.3	18.6%
Genetech	$3.30	$0.72	21.82%	$4.62	$0.95	20.56%	46.6	$1.3	19.0%
			16.16%			16.63%			16.8%

2.3.1. Early Termination Strategies

Competitive economic forces have led to productivity and quality improvement mandates for all pharmaceutical companies, and as the cost of developing new medicines rises, decisions regarding continuing or terminating unpromising R&D programs have become increasingly critical. Reasons for terminating unpromising new drugs and the time to terminate are presented in Figure 28-3. Although safety and efficacy considerations have historically led to decisions to terminate clinical programs, economic factors—apart from safety and efficacy—are currently foremost in determining the viability of an investigational drug.[21]

2.3.2. Exportation of Clinical Trials

In an environment of increasing numbers of clinical trials every year, the pool of principal study investigators has dropped in the United States by 11% between 2001 and 2003. Not only has this pool decreased in size but also it has become significantly more male (even more male than the percentage of males in the population of board-certified physicians in the United States) and more regional. In other words, there has been a significant decline of principal study investigators practicing in regions with declining population, which potentially diminishes scientific and economic benefits to these areas. Conversely, the number of principal investigators outside the United States increased by 8% during the same period of time. In response to this shift in principal investigators and the concomitant availability of study subjects abroad, there has been a continued exportation of clinical trials from the United States to those areas with increasing populations of principal investigators and resulting patient populations.[22]

The impact of this shift on pharmaceutical companies is that, by placing studies offshore, their clinical trials can be conducted more efficiently with respect to both time and expenses to the detriment of the U.S. economy.

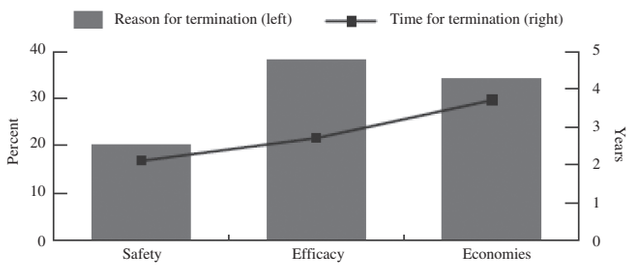

FIGURE 28-3 Reasons for terminating unpromising new drugs and time to termination. Source: Tufts Center for the Study of Drug Development.

2.3.3. Cost Containment

The cost of drug development has increased 250% in the past 10 years. The price of medicines has reflected this increase despite the fact that only 3 approved new medicines in 10 return their development costs to the pharmaceutical company. Growing pressures to contain costs from government and private health benefits organizations in the United States and pricing and reimbursement authorities abroad will continue to levy pressure on pharmaceutical companies to move new drugs with clear advantages in safety, efficacy, or economic value to market quickly. In addition, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, launched in 2006, is causing increased pressure on pharmaceutical companies by health care plans and pharmacy benefit managers to exhibit advantageous cost and benefit profiles of their products in order to add them to their formularies.[21]

Financial pressures are generated not only by the pricing of new medicines but also by the robust generic medicine companies positioned to manufacture and sell innovator medicines as patents expire. In recent years, 30–40 innovative drugs with worldwide sales exceeding $10 billion lost patent protection each year and were subject to generic entry.[19]

The United States has a vital generic drug industry, largely as a result of the 1984 passage of the Waxman–Hatch Act, which facilitates entry of generic products as the patents for innovative products expire. Generic product entry drives down the sales of the nonpatent-protected innovator products and drives down the prices of the generic counterparts through market competition. Strong protection of intellectual property (patent protection) preserves the incentive to develop improved treatments, whereas the cost of new treatments declines rapidly after patents expire, leading to cost containment.[19]

2.3.4. Accelerated Approval of Medications (Fast Track)

Fast track programs became available under the FDA Modernization Act of 1997 and are designed to facilitate development and expedited review of new drugs intended to treat serious or life-threatening conditions and to demonstrate the potential to address unmet medical needs. Seriousness with regard to fast track designation is defined by the FDA as a disease that "impacts such factors as survival, day-to-day

functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." Examples include AIDS and HIV, Alzheimer's disease, angina pectoris, heart failure, and cancer.[23]

In order for a product to be considered for the fast track regulatory approval process, "it must not only be used in patients with a serious condition, it must be intended to treat a serious aspect of that condition."[23] The following are examples of products that might meet these criteria:

- Therapeutic products directed at some aspect of a serious condition
- Diagnostic products used to improve diagnosis or detection of a condition with the presumption that the improvements in diagnosis or detection would lead to improved outcome
- Preventive products used for their ability to prevent serious manifestation(s) of a condition or to prevent a condition thereby preventing its serious consequences
- Products intended to ameliorate or prevent a serious side effect of another therapy treating a serious condition
- Therapeutic products with the ability to treat a condition while avoiding the serious sequelae of currently accepted treatments of the condition[23]

In order to qualify for the FDA fast track program, a product also must demonstrate the potential to address unmet medical needs in any of the following scenarios:

- There is no available therapy for the condition.
- There is available therapy for the condition, but
  the new therapy exhibits superiority used alone or in combination with other therapies in morbidity end point controlled clinical trial(s);
  the new therapy exhibits a positive effect on progressive disability that available therapy does not exhibit;
  the new therapy provides benefit in patients who are unable to tolerate or are unresponsive to available therapy;
  the new therapy provides benefit(s) similar to available therapy while avoiding serious toxicity present in available therapy or common, less serious toxicity that causes discontinuation of available therapy; or
  the new therapy provides similar benefit to available therapy but exhibits improvement of some factor (e.g., compliance or convenience) that leads to improved effects on serious outcomes.
- The only available therapy had accelerated approval (either on the basis of an effect on a surrogate end point or for restricted distribution).[23]

In summary, the FDA's Fast Track Drug Development Program is an example of industry and regulators working together to solve a problem to the benefit of each party. As more investigational medicines are reviewed under the FDA's fast track designation, the resultant efficiencies should lead to a speedier, less expensive drug development process, which in turn should lead to more accessibility to new medicines.

3. INDUSTRY OUTLOOK

The pharmaceutical industry continues to be an exciting and innovative industry in which huge strides in medical advancement will continue to be realized in the years to come. Despite the innovations still to be made, the pharmaceutical industry faces serious challenges both from government regulators and the marketplace.

As traditional pharmaceutical companies continue to streamline the new drug development process and many incorporate biotechnological methodologies into at least part of their research effort, they will not only continue to develop new chemical entities for large portions of the population but also be able to develop drugs and biologicals used to treat small, unserved or underserved portions of the population, as biotechnology companies currently do, thus relieving, in part, some of the hurdles they have traditionally faced.

Biotechnology companies will likely prosper in the next few years as they continue to engage in innovative R&D strategies and investigate therapeutic and diagnostic products with high approval success rates. Their successes are likely to occur in the areas of serious and life-threatening diseases, due in part to the availability of fast track designation by the FDA.[18,21] Successes are likely to come in the areas of:

- diseases and conditions eligible for fast track designation;
- recombinant therapeutics currently in development (more than 30 are likely to be approved by the FDA in the short term);
- innovative and orphan therapeutics, if firms capitalize on scientific advice available from the FDA and its counterpart in Europe, the European Agency for Evaluation of Medicinal Products; and
- increasing numbers of oncology monoclonal antibodies will enter clinical trials due to recent successful launches.[18,21]

The outlook for biotechnology companies is strong. Biotechnology companies tend to have fewer problems amassing patients for their studies. These patients actively seek out promising medicines for their unmet needs through Web searches and patient advocacy groups. Since these patients are not already taking effective therapy for their medical conditions, they are much more willing to participate in clinical trials than are patients already being treated with available therapy.[24]

3.1. Public–Private Opportunities

Although some biopharmaceutical companies conduct their entire drug discovery and development programs in-house, many companies engage cooperatively with other organizations to share their expertise in drug discovery and development. These partnerships may take the form of licensing agreements between large pharmaceutical companies and biotechnology companies, in which the larger company typically conducts the large, expensive clinical trials of a promising investigational product discovered by a biotechnology firm. Other types of partnerships also exist between a pharmaceutical company and academic medical centers and/or government research agencies.[21]

Through these public–private partnerships, each entity brings its unique resources and strengths to the partnership (including intellectual property and other proprietary materials, experimental compounds, scientific expertise, and financial resources), which results in a more efficient development process and ultimately a better product than either partner could accomplish alone. Public–private partnerships have become a model for advancing science and communicating results of medical advances. As increasingly complex biomedical problems are addressed, strategic partnerships between pharmaceutical companies, government research agencies, academic medical centers, and other research centers will become increasingly important.[25]

4. SUMMARY

The successes and challenges the pharmaceutical industry faces in its conduct of clinical trials are in some ways similar and in many ways different from those faced by nonindustry participants in clinical research. Changes in the way clinical trials are conducted are beginning to reflect these issues and should continue to do so. Since the overwhelming percentage of the world's new medicines are developed by U.S. pharmaceutical companies, it is in the regulators' and the public's best interest to facilitate pharmaceutical research and development in a manner that foremost protects patient safety while providing new medicines to promote patient health and well-being.

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