Goodman & Gilman's

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS

13TH EDITION

LAURENCE L. BRUNTON
RANDA HILAL-DANDAN
BJÖRN C. KNOLLMANN

Mc Graw Hill Education

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THIRTEENTH EDITION

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THIRTEENTH EDITION

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In Memoriam

Alfred Goodman Gilman

(1941-2015)

Mentor, teacher, researcher, Nobel laureate, raconteur, mensch,
and longtime editor of this book

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Preface

The first edition of this book appeared in 1941, the product of a collaboration between two friends and professors at Yale, Louis Goodman and Alfred Gilman. Their purpose, stated in the preface to that edition, was to correlate pharmacology with related medical sciences, to reinterpret the actions and uses of drugs in light of advances in medicine and the basic biomedical sciences, to emphasize the applications of pharmacodynamics to therapeutics, and to create a book that would be useful to students of pharmacology and to physicians. We continue to follow these principles in the 13th edition.

The 1st edition was quite successful despite its high price, $12.50, and soon became known as the "blue bible of pharmacology." The book was evidence of the deep friendship between its authors, and when the Gilmans' son was born in 1941, he was named Alfred Goodman Gilman. World War II and the relocation of both authors—Goodman to Utah, Gilman to Columbia—postponed a second edition until 1955. The experience of writing the second edition during a period of accelerating basic research and drug development persuaded the authors to become editors, relying on experts whose scholarship they trusted to contribute individual chapters, a pattern that has been followed ever since.

Alfred G. Gilman, the son, served as an associate editor for the 5th edition (1975), became the principal editor for the 6th (1980), 7th (1985), and 8th (1990) editions, and consulting editor for the 9th and 10th editions that were edited by Lee Limbird and Joel Hardman. After an absence in the 11th edition, Al Gilman agreed to co-author the introductory chapter in the 12th edition. His final contribution to G&G, a revision of that chapter, is the first chapter in this edition, which we dedicate to his memory.

A multi-authored text of this sort grows by accretion, posing challenges to editors but also offering 75 years of wisdom, memorable pearls, and flashes of wit. Portions of prior editions persist in the current edition, and we have given credit to recent former contributors at the end of each chapter. Such a text also tends to grow in length with each edition, as contributors add to existing text and as pharmacotherapy advances. To keep the length manageable and in a single volume, Dr. Randa Hilal-Dandan and I prepared a shortened version of each chapter and then invited contributors to add back old material that was essential and to add new material. We also elected to discard the use of extract (very small) type and to use more figures to explain signaling pathways and mechanisms of drug action. Not wanting to favor one company's preparation of an agent over that of another, we have ceased to use trade names except as needed to refer to drug combinations or to distinguish multiple formulations of the same agent with distinctive pharmacokinetic or pharmacodynamic properties. Counter-balancing this shortening are five new chapters that reflect advances in the therapeutic manipulation of the immune system, the treatment of viral hepatitis, and the pharmacotherapy of cardiovascular disease and pulmonary artery hypertension.

Editing such a book brings into view a number of overarching issues: Over-prescribing of antibiotics and their excessive use in agricultural animal husbandry continues to promote the development of antimicrobial resistance; the application of CRISPR/cas9 will likely provide new therapeutic avenues; global warming and the sheer size of the human population require medical scientists and practitioners to promote remedial and preventive action based on data, not ideology.

A number of people have made invaluable contributions to the preparation of this edition. My thanks to Randa Hilal-Dandan and Bjorn Knollmann for their editorial work; to Harriet Lebowitz of McGraw-Hill, who guided our work, prescribed the updated style, and kept the project moving to completion; to Vastavikta Sharma of Cenveo Publishers Services, who oversaw the copy editing, typesetting, and preparation of the artwork; to Nelda Murri, our consulting pharmacist, whose familiarity with clinical pharmacy is evident throughout the book; to James Shanahan, publisher at McGraw-Hill, for supporting the project; and to the many readers who have written to critique the book and offer suggestions.

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Section I

General Principles

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Chapter 1

Drug Invention and the Pharmaceutical Industry

Suzanne M. Rivera and Alfred Goodman Gilman*

The first edition of *Goodman & Gilman*, published in 1941, helped to organize the field of pharmacology, giving it intellectual validity and an academic identity. That edition began: "The subject of pharmacology is a broad one and embraces the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate, and excretion, and therapeutic uses of drugs. A *drug* may be broadly defined as any chemical agent that affects living protoplasm, and few substances would escape inclusion by this definition." This General Principles section provides the underpinnings for these definitions by exploring the processes of drug invention, development, and regulation, followed by the basic properties of the interactions between the drug and biological systems: *pharmacodynamics*, *pharmacokinetics* (including drug transport and metabolism), and *pharmacogenomics*, with a brief foray into *drug toxicity and poisoning*. Subsequent sections deal with the use of drugs as therapeutic agents in human subjects.

Use of the term *invention* to describe the process by which a new drug is identified and brought to medical practice, rather than the more conventional term *discovery,* is intentional. Today, useful drugs are rarely discovered hiding somewhere waiting to be found. The term *invention* emphasizes the process by which drugs are sculpted and brought into being based on experimentation and optimization of many independent properties; there is little serendipity.

From Early Experiences With Plants to Modern Chemistry

The human fascination—and sometimes infatuation—with chemicals that alter biological function is ancient and results from long experience with and dependence on plants. Because most plants are root bound, many of them produce harmful compounds for defense that animals have learned to avoid and humans to exploit (or abuse).

Earlier editions of this text described examples: the appreciation of coffee (caffeine) by the prior of an Arabian convent, who noted the behavior of goats that gamboled and frisked through the night after eating the berries of the coffee plant; the use of mushrooms and the deadly nightshade plant by professional poisoners; of belladonna ("beautiful lady") to dilate pupils; of the Chinese herb ma huang (containing ephedrine) as a circulatory stimulant; of curare by South American Indians to paralyze and kill animals hunted for food; and of poppy juice (opium) containing morphine (from the Greek *Morpheus*, the God of dreams) for pain relief and control of dysentery. Morphine, of course, has well-known addicting properties, mimicked in some ways by other problematic ("recreational") natural products—nicotine, cocaine, and ethanol.

Although terrestrial and marine organisms remain valuable sources of compounds with pharmacological activities, drug invention became more allied with synthetic organic chemistry as that discipline flourished over the past 150 years, beginning in the dye industry. Dyes are colored compounds with selective affinity for biological tissues. Study of these interactions stimulated Paul Ehrlich to postulate the existence of chemical receptors in tissues that interacted with and "fixed" the dyes. Similarly, Ehrlich thought that unique receptors on microorganisms or parasites might react specifically with certain dyes and that such selectivity could spare normal tissue. Ehrlich's work culminated in the invention of arsphenamine in 1907, which was patented as "salvarsan," suggestive of the hope that the chemical would be the salvation of humankind. This and other organic arsenicals were used for the chemotherapy of syphilis until the discovery of penicillin. The work of Gerhard Domagk demonstrated that another dye, prontosil (the first clinically useful sulfonamide), was dramatically effective in treating streptococcal infections, launching the era of antimicrobial chemotherapy.

The collaboration of pharmacology with chemistry on the one hand and with clinical medicine on the other has been a major contributor to the effective treatment of disease, especially since the middle of the 20th century.

Sources of Drugs

Small Molecules Are the Tradition

With the exception of a few naturally occurring hormones (e.g., insulin), most drugs were small organic molecules (typically <500 Da) until

*Deceased, December 23, 2015. AGG served on the Board of Directors of Regeneron Pharmaceuticals, Inc., a potential conflict of interest.

Abbreviations

ADME: absorption, distribution, metabolism, excretion
AHFS-DI: American Hospital Formulary Service-Drug Information
BLA: Biologics License Application
CDC: Centers for Disease Control and Prevention
CDER: Center for Drug Evaluation and Research
DHHS: U.S. Department of Health and Human Services
FDA: U.S. Food and Drug Administration
HCV: hepatitis C virus
HMG CoA: 3-hydroxy-3-methylglutaryl coenzyme A
IND: Investigational New Drug
LDL: low-density lipoprotein
NDA: New Drug Application
NIH: National Institutes of Health
NMEs: New Molecular Entities
NMR: nuclear magnetic resonance
PCSK9: proprotein convertase subtilisin/kexin type 9
PDUFA: Prescription Drug User Fee Act
PhRMA: Pharmaceutical Research and Manufacturers of America
R&D: research and development
SCHIP: State Children's Health Insurance Program
siRNAs: small interfering RNAs

recombinant DNA technology permitted synthesis of proteins by various organisms (bacteria, yeast) and mammalian cells. The usual approach to invention of a small-molecule drug is to screen a collection of chemicals ("library") for compounds with the desired features. An alternative is to synthesize and focus on close chemical relatives of a substance known to participate in a biological reaction of interest (e.g., congeners of a specific enzyme substrate chosen to be possible inhibitors of the enzymatic reaction), a particularly important strategy in the discovery of anticancer drugs.

Drug discovery in the past often resulted from serendipitous observations of the effects of plant extracts or individual chemicals on animals or humans; today's approach relies more on high-throughput screening of libraries containing hundreds of thousands or even millions of compounds for their capacity to interact with a specific molecular target or elicit a specific biological response. Ideally, the target molecules are of human origin, obtained by transcription and translation of the cloned human gene. The potential drugs that are identified in the screen ("hits") are thus known to react with the human protein and not just with its relative (ortholog) obtained from the mouse or another species.

Among the variables considered in screening are the "drugability" of the target and the stringency of the screen in terms of the concentrations of compounds that are tested. *Drugability* refers to the ease with which the function of a target can be altered in the desired fashion by a small organic molecule. If the protein target has a well-defined binding site for a small molecule (e.g., a catalytic or allosteric site), chances are excellent that hits will be obtained. If the goal is to employ a small molecule to mimic or disrupt the interaction between two proteins, the challenge is much greater.

From Hits to Leads

Initial hits in a screen are rarely marketable drugs, often having modest affinity for the target and lacking the desired specificity and pharmacological properties. Medicinal chemists synthesize derivatives of the hits, thereby defining the structure-activity relationship and optimizing parameters such as affinity for the target, agonist/antagonist activity, permeability across cell membranes, absorption and distribution in the body, metabolism, and unwanted effects.

This approach was driven largely by instinct and trial and error in the past; modern drug development frequently takes advantage of determination of a high-resolution structure of the putative drug bound to its target. X-ray crystallography offers the most detailed structural information if the target protein can be crystallized with the lead drug bound to it. Using techniques of molecular modeling and computational chemistry, the structure provides the chemist with information about substitutions likely to improve the "fit" of the drug with the target and thus enhance the affinity of the drug for its target. Nuclear magnetic resonance (NMR) studies of the drug-receptor complex also can provide useful information (albeit usually at lower resolution), with the advantage that the complex need not be crystallized.

The holy grail of this approach to drug invention is to achieve success entirely through computation. Imagine a database containing detailed chemical information about millions of chemicals and a second database containing detailed structural information about all human proteins. The computational approach is to "roll" all the chemicals over the protein of interest to find those with high-affinity interactions. The dream becomes bolder if we acquire the ability to roll the chemicals that bind to the target of interest over all other human proteins to discard compounds that have unwanted interactions. Finally, we also will want to predict the structural and functional consequences of a drug binding to its target (a huge challenge), as well as all relevant pharmacokinetic properties of the molecules of interest. Indeed, computational approaches have suggested new uses for old drugs and offered explanations for recent failures of drugs in the later stages of clinical development (e.g., torcetrapib; see Box 1-2) (Xie et al., 2007, 2009).

Large Molecules Are Increasingly Important

Protein therapeutics were uncommon before the advent of recombinant DNA technology. Insulin was introduced into clinical medicine for the treatment of diabetes following the experiments of Banting and Best in 1921. Insulins purified from porcine or bovine pancreas are active in humans, although antibodies to the foreign proteins are occasionally problematic. Growth hormone, used to treat pituitary dwarfism, exhibits more stringent species specificity. Only the human hormone could be used after purification from pituitary glands harvested during autopsy, and such use had its dangers—some patients who received the human hormone developed Creutzfeldt-Jakob disease (the human equivalent of mad cow disease), a fatal degenerative neurological disease caused by prion proteins that contaminated the drug preparation. Thanks to gene cloning and the production of large quantities of proteins by expressing the cloned gene in bacteria or eukaryotic cells, protein therapeutics now use highly purified preparations of human (or humanized) proteins. Rare proteins can be produced in quantity, and immunological reactions are minimized. Proteins can be designed, customized, and optimized using genetic engineering techniques. Other types of macromolecules may also be used therapeutically. For example, antisense oligonucleotides are used to block gene transcription or translation, as are siRNAs.

Proteins used therapeutically include hormones; growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor); cytokines; and a number of monoclonal antibodies used in the treatment of cancer and autoimmune diseases (Chapters 34–36 and 67). Murine monoclonal antibodies can be "humanized" (by substituting human for mouse amino acid sequences). Alternatively, mice have been engineered by replacement of critical mouse genes with their human equivalents, such that they make completely human antibodies. Protein therapeutics are administered parenterally, and their receptors or targets must be accessible extracellularly.

Targets of Drug Action

Early drugs came from observation of the effects of plants after their ingestion by animals, with no knowledge of the drug's mechanism or site of action. Although this approach is still useful (e.g., in screening for the capacity of natural products to kill microorganisms or malignant cells), modern drug invention usually takes the opposite approach, starting with

a statement (or hypothesis) that a certain protein or pathway plays a critical role in the pathogenesis of a certain disease, and that altering the protein's activity would be effective against that disease. Crucial questions arise:

- Can one find a drug that will have the desired effect against its target?
- Does modulation of the target protein affect the course of disease?
- Does this project make sense economically?

The effort expended to find the desired drug will be determined by the degree of confidence in the answers to the last two questions.

Is the Target Drugable?

The drugability of a target with a low-molecular-weight organic molecule relies on the presence of a binding site for the drug that exhibits considerable affinity and selectivity.

If the target is an enzyme or a receptor for a small ligand, one is encouraged. If the target is related to another protein that is known to have, for example, a binding site for a regulatory ligand, one is hopeful. However, if the known ligands are large peptides or proteins with an extensive set of contacts with their receptor, the challenge is much greater. If the goal is to disrupt interactions between two proteins, it may be necessary to find a "hot spot" that is crucial for the protein-protein interaction, and such a region may not be detected. Accessibility of the drug to its target also is critical. Extracellular targets are intrinsically easier to approach, and, in general, only extracellular targets are accessible to macromolecular drugs.

Has the Target Been Validated?

The question of whether the target has been validated is obviously a critical one. A negative answer, frequently obtained only retrospectively, is a common cause of failure in drug invention (Box 1–1). Modern techniques of molecular biology offer powerful tools for validation of potential drug targets, to the extent that the biology of model systems resembles human biology. Genes can be inserted, disrupted, and altered in mice. One can thereby create models of disease in animals or mimic the effects of long-term disruption or activation of a given biological process. If, for example, disruption of the gene encoding a specific enzyme or receptor has a beneficial effect in a valid murine model of a human disease, one may believe that the potential drug target has been validated. Mutations in humans also can provide extraordinarily valuable information.

For example, loss-of-function mutations in the *PCSK9* gene (encoding proprotein convertase subtilisin/kexin type 9) greatly lower concentrations of LDL cholesterol in blood and reduce the risk of myocardial infarction (Horton et al., 2009; Poirier and Mayer, 2013). Based on these findings, two companies now market antibodies that inhibit the action of *PCSK9*. These antibodies lower the concentration of LDL cholesterol in blood substantially and are essentially additive to the effects of statins; long-term outcome studies are in progress to determine whether the risk of significant cardiovascular events also is reduced. Additional molecules are in the queue.

BOX 1–1 ■ Target Validation: The Lesson of Leptin

Biological systems frequently contain redundant elements or can alter expression of drug-regulated elements to compensate for the effect of the drug. *In general, the more important the function, the greater the complexity of the system.* For example, many mechanisms control feeding and appetite, and drugs to control obesity have been notoriously difficult to find. The discovery of the hormone leptin, which suppresses appetite, was based on mutations in mice that cause loss of either leptin or its receptor; either kind of mutation results in enormous obesity in both mice and people. Leptin thus appeared to be a marvelous opportunity to treat obesity. However, on investigation, it was discovered that obese individuals have high circulating concentrations of leptin and appear insensitive to its action.

Is This Drug Invention Effort Economically Viable?

Drug invention and development is expensive (see Table 1-1), and economic realities influence the direction of pharmaceutical research. For example, investor-owned companies generally cannot afford to develop products for rare diseases or for diseases that are common only in economically underdeveloped parts of the world. Funds to invent drugs targeting rare diseases or diseases primarily affecting developing countries (especially parasitic diseases) often come from taxpayers or wealthy philanthropists.

Additional Preclinical Research

Following the path just described can yield a potential drug molecule that interacts with a validated target and alters its function in the desired fashion. Now, one must consider all aspects of the molecule in question—its affinity and selectivity for interaction with the target; its pharmacokinetic properties (ADME); issues of its large-scale synthesis or purification; its pharmaceutical properties (stability, solubility, questions of formulation); and its safety. One hopes to correct, to the extent possible, any obvious deficiencies by modification of the molecule itself or by changes in the way the molecule is presented for use.

Before being administered to people, potential drugs are tested for general toxicity by long-term monitoring of the activity of various systems in two species of animals, generally one rodent (usually the mouse) and one nonrodent (often the rabbit). Compounds also are evaluated for carcinogenicity, genotoxicity, and reproductive toxicity (see Chapter 4). In vitro and ex vivo assays are used when possible, both to spare animals and to minimize cost. If an unwanted effect is observed, an obvious question is whether it is mechanism based (i.e., caused by interaction of the drug with its intended target) or caused by an off-target effect of the drug, which might be minimized by further optimization of the molecule.

Before the drug candidate can be administered to human subjects in a clinical trial, the sponsor must file an IND application, a request to the U.S. FDA (see "Clinical Trials") for permission to use the drug for human research. The IND describes the rationale and preliminary evidence for efficacy in experimental systems, as well as pharmacology, toxicology, chemistry, manufacturing, and so forth. It also describes the plan (protocol) for investigating the drug in human subjects. The FDA has 30 days to review the IND application, by which time the agency may disapprove it, ask for more data, or allow initial clinical testing to proceed.

Clinical Trials

Role of the FDA

The FDA is a federal regulatory agency within the U.S. DHHS. It is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation (FDA, 2014). The FDA also is responsible for advancing public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable and by helping people obtain the accurate, science-based information they need to use medicines and foods to improve their health.

New governmental regulations often result from tragedies. The first drug-related legislation in the U.S., the Federal Food and Drug Act of 1906, was concerned only with the interstate transport of adulterated or misbranded foods and drugs. There were no obligations to establish drug efficacy or safety. This act was amended in 1938 after the deaths of over 100 children from "elixir sulfanilamide," a solution of sulfanilamide in diethylene glycol, an excellent but highly toxic solvent and an ingredient in antifreeze. The enforcement of the amended act was entrusted to the FDA, which began requiring toxicity studies as well as approval of an NDA (see "The Conduct of Clinical Trials") before a drug could be promoted and distributed. Although a new drug's safety had to be demonstrated, no proof of efficacy was required.

In the 1960s, thalidomide, a hypnotic drug with no obvious advantages over others, was introduced in Europe. Epidemiological research eventually established that this drug, taken early in pregnancy, was responsible for an epidemic of what otherwise is a relatively rare and severe birth defect, phocomelia, in which limbs are malformed. In reaction to this catastrophe, the U.S. Congress passed the Harris-Kefauver amendments to the Food, Drug, and Cosmetic Act in 1962. These amendments established the requirement for proof of efficacy as well as documentation of relative safety in terms of the risk-to-benefit ratio for the disease entity to be treated (the more serious the disease, the greater the acceptable risk).

Today, the FDA faces an enormous challenge, especially in view of the widely held belief that its mission cannot possibly be accomplished with the resources allocated by Congress. Moreover, harm from drugs that cause unanticipated adverse effects is not the only risk of an imperfect system; harm also occurs when the approval process delays the approval of a new drug with important beneficial effects.

The Conduct of Clinical Trials

Clinical trials of drugs are designed to acquire information about the pharmacokinetic and pharmacodynamic properties of a candidate drug in humans. Efficacy must be proven and an adequate margin of safety established for a drug to be approved for sale in the U.S.

The U.S. NIH identifies seven ethical principles that must be satisfied before a clinical trial can begin:

1. Social and clinical value
2. Scientific validity
3. Fair selection of subjects
4. Informed consent
5. Favorable risk-benefit ratio
6. Independent review
7. Respect for potential and enrolled subjects (NIH, 2011).

The FDA-regulated clinical trials typically are conducted in four phases. Phases I-III are designed to establish safety and efficacy, while phase IV postmarketing trials delineate additional information regarding new indications, risks, and optimal doses and schedules. Table 1–1 and Figure 1–1 summarize the important features of each phase of clinical trials; note the attrition at each successive stage over a relatively long and costly process. When initial phase III trials are complete, the sponsor (usually a pharmaceutical company) applies to the FDA for approval to market the drug; this application is called either an NDA or a BLA. These applications contain comprehensive information, including individual case report forms from the hundreds or thousands of individuals who have received the drug during its phase III testing. Applications are reviewed by teams of specialists, and the FDA may call on the help of panels of external experts in complex cases.

Under the provisions of the PDUFA (enacted in 1992 and renewed every 5 years, most recently in 2012), pharmaceutical companies now provide a significant portion of the FDA budget via user fees, a legislative effort to expedite the drug approval review process by providing increased resources. The PDUFA also broadened the FDA's drug safety program and increased resources for review of television drug advertising. Under the PDUFA, once an NDA is submitted to the FDA, review typically takes 6–10 months. During this time, numerous review functions are usually performed, including advisory committee meetings, amendments, manufacturing facility inspections, and proprietary name reviews (FDA, 2013a). Before a drug is approved for marketing, the company and the FDA must agree on the content of the "label" (package insert)—the official prescribing information. This label describes the approved indications for use of the drug and clinical pharmacological information, including dosage, adverse reactions, and special warnings and precautions (sometimes posted in a "black box").

Promotional materials used by pharmaceutical companies cannot deviate from information contained in the package insert. Importantly, the physician is not bound by the package insert; a physician in the U.S. *may* legally prescribe a drug for any purpose that he or she deems reasonable. However, third-party payers (insurance companies, Medicare, and so on) generally will not reimburse a patient for the cost of a drug used for an "off-label" indication unless the new use is supported by a statutorily named compendium (e.g., the AHFS-DI). Furthermore, a physician may be vulnerable to litigation if untoward effects result from an unapproved use of a drug.

Determining "Safe" and "Effective"

Demonstrating efficacy to the FDA requires performing "adequate and well-controlled investigations," generally interpreted to mean two replicate clinical trials that are usually, but not always, randomized, double blind, and placebo (or otherwise) controlled.

Is a placebo the proper control? The World Medical Association's *Declaration of Helsinki* (World Medical Association 2013) discourages use of placebo controls when an alternative treatment is available for comparison because of the concern that study participants randomized to placebo in such a circumstance would, in effect, be denied treatment during the conduct of the trial.

What must be measured in the trials? In a straightforward trial, a readily quantifiable parameter (a secondary or surrogate end point), thought to be predictive of relevant clinical outcomes, is measured in matched drug- and placebo-treated groups. Examples of surrogate end points include

TABLE 1–1 ■ TYPICAL CHARACTERISTICS OF THE VARIOUS PHASES OF THE CLINICAL TRIALS REQUIRED FOR MARKETING OF NEW DRUGS

PHASE I FIRST IN HUMAN	PHASE II FIRST IN PATIENT	PHASE III MULTISITE TRIAL	PHASE IV POSTMARKETING SURVEILLANCE
10–100 participants	50–500 participants	A few hundred to a few thousand participants	Many thousands of participants
Usually healthy volunteers; occasionally patients with advanced or rare disease	Patient-subjects receiving experimental drug	Patient-subjects receiving experimental drug	Patients in treatment with approved drug
Open label	Randomized and controlled (can be placebo controlled); may be blinded	Randomized and controlled (can be placebo controlled) or uncontrolled; may be blinded	Open label
Safety and tolerability	Efficacy and dose ranging	Confirm efficacy in larger population	Adverse events, compliance, drug-drug interactions
1–2 years	2–3 years	3–5 years	No fixed duration
U.S. $10 million	U.S. $20 million	U.S. $50–100 million	—
Success rate: 50%	Success rate: 30%	Success rate: 25%–50%	—

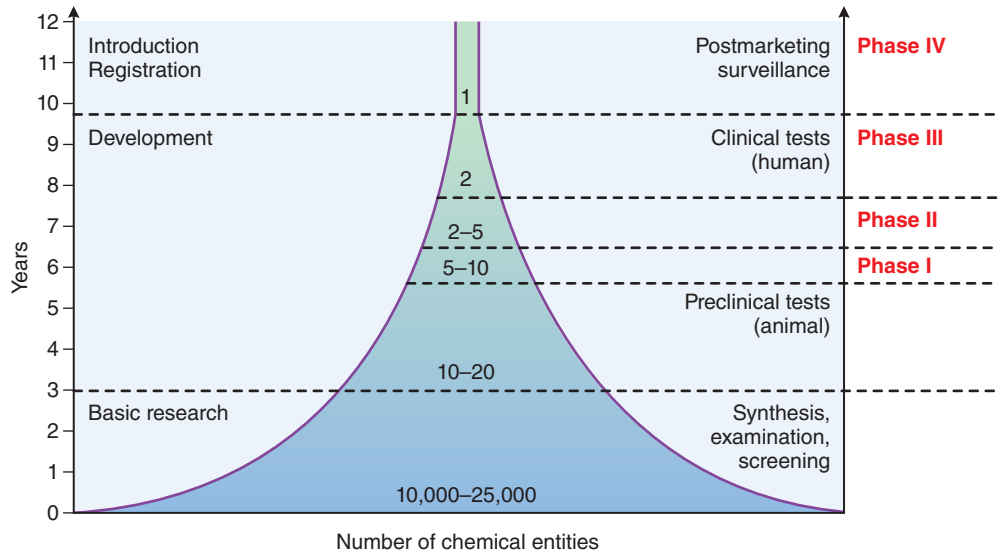

Figure 1–1 *The phases, time lines, and attrition that characterize the invention of new drugs.* See also Table 1–1.

LDL cholesterol as a predictor of myocardial infarction, bone mineral density as a predictor of fractures, or hemoglobin A_{1c} as a predictor of the complications of diabetes mellitus. More stringent trials would require demonstration of reduction of the incidence of myocardial infarction in patients taking a candidate drug in comparison with those taking an HMG CoA reductase inhibitor (statin) or other LDL cholesterol-lowering agent or reduction in the incidence of fractures in comparison with those taking a bisphosphonate. Use of surrogate end points significantly reduces cost and time required to complete trials, but there are many mitigating factors, including the significance of the surrogate end point to the disease that the candidate drug is intended to treat.

Some of the difficulties are well illustrated by experiences with ezetimibe, a drug that inhibits absorption of cholesterol from the gastrointestinal tract and lowers LDL cholesterol concentrations in blood, especially when used in combination with a statin. Lowering of LDL cholesterol was assumed to be an appropriate surrogate end point for the effectiveness of ezetimibe to reduce myocardial infarction and stroke, and the drug was approved based on such data. Surprisingly, a subsequent clinical trial (ENHANCE) demonstrated that the combination of ezetimibe and a statin did not reduce intima media thickness of carotid arteries (a more direct measure of subendothelial cholesterol accumulation) compared with the statin alone, despite the fact that the drug combination lowered LDL cholesterol concentrations substantially more than did either drug alone (Kastelein et al., 2008).

Critics of ENHANCE argued that the patients in the study had familial hypercholesterolemia, had been treated with statins for years, and did not have carotid artery thickening at the initiation of the study. Should ezetimibe have been approved? Must we return to measurement of true clinical end points (e.g., myocardial infarction) before approval of drugs that lower cholesterol by novel mechanisms? The costs involved in such extensive and expensive trials must be borne somehow (see below). A follow-up 7-year study involving over 18,000 patients (IMPROVE-IT) vindicated the decision to approve ezetimibe (Jarcho and Keaney, 2015). Taken in conjunction with a statin, the drug significantly reduced the incidence of myocardial infarction and stroke in high-risk patients (Box 1–2).

No drug is totally safe; all drugs produce unwanted effects in at least some people at some dose. Many unwanted and serious effects of drugs occur so infrequently, perhaps only once in several thousand patients, that they go undetected in the relatively small populations (a few thousand) in the standard phase III clinical trial (see Table 1–1). To detect and verify that such events are, in fact, drug-related would require administration of the drug to tens or hundreds of thousands of people during clinical trials, adding enormous expense and time to drug development and delaying access to potentially beneficial therapies. In general, the true spectrum and incidence of untoward effects become known only after a drug is released to the broader market and used by a large number of people (phase IV, postmarketing surveillance). Drug development costs and drug prices could be reduced substantially if the public were willing to accept more risk. This would require changing the way we think about a pharmaceutical company's liability for damages from an unwanted effect of a drug that was not detected in clinical trials deemed adequate by the FDA. While the concept is obvious, many lose sight of the fact that extremely severe unwanted effects of a drug, including death, may be deemed acceptable if its therapeutic effect is sufficiently unique and valuable. Such dilemmas are not simple and can become issues for great debate.

Several strategies exist to detect adverse reactions after marketing of a drug. Formal approaches for estimation of the magnitude of an adverse drug response include the follow-up or "cohort" study of patients who are receiving a particular drug; the "case-control" study, in which the frequency of drug use in cases of adverse responses is compared to controls; and meta-analysis of pre- and postmarketing studies. Voluntary reporting of adverse events has proven to be an effective way to generate an early signal that a drug may be causing an adverse reaction (Aagard and Hansen, 2009). The primary sources for the reports are responsible, alert physicians; third-party payers (pharmacy benefit managers, insurance companies) and consumers also play important roles. Other useful sources are nurses, pharmacists, and students in these disciplines. In addition, hospital-based pharmacy and therapeutics committees and quality assurance committees frequently are charged with monitoring adverse drug reactions in hospitalized patients. In 2013, the reporting system in the U.S., called *MedWatch,* celebrated its 20th anniversary and announced improvements designed to encourage reporting by consumers (FDA, 2013b). The simple forms for reporting may be obtained 24 hours a day, 7 days a week, by calling 800-FDA-1088; alternatively, adverse reactions

BOX 1–2 ■ A Late Surprise in the Development of a Blockbuster

Torcetrapib elevates high-density lipoprotein (HDL) cholesterol (the "good cholesterol"), and higher levels of HDL cholesterol are statistically associated with (are a surrogate end point for) a lower incidence of myocardial infarction. Surprisingly, clinical administration of torcetrapib caused a significant *increase* in mortality from cardiovascular events, ending a development path of 15 years and $800 million. In this case, approval of the drug based on this secondary end point would have been a mistake (Cutler, 2007). A computational systems analysis suggested a mechanistic explanation of this failure (Xie et al., 2009).

can be reported directly using the Internet (http://www.fda.gov/Safety/MedWatch/default.htm). Health professionals also may contact the pharmaceutical manufacturer, who is legally obligated to file reports with the FDA.

Personalized (Individualized, Precision) Medicine

Drug inventors strive to "fit" the drug to the individual patient. To realize the full potential of this approach, however, requires intimate knowledge of the considerable heterogeneity of both the patient population and the targeted disease process. Why does one antidepressant appear to ameliorate depression in a given patient, while another with the same or very similar presumed mechanism of action does not? Is this a difference in the patient's response to the drug; in patient susceptibility to the drug's unwanted effects; in the drug's ADME; or in the etiology of the depression? By contrast, how much of this variability is attributable to environmental factors and possibly their interactions with patient-specific genetic variability? Recent advances, especially in genetics and genomics, provide powerful tools for understanding this heterogeneity. The single most powerful tool for unraveling these myriad mysteries is the ability to sequence DNA rapidly and economically. The cost of sequencing a human genome has fallen by six orders of magnitude since the turn of the 21st century, and the speed of the process has increased correspondingly. The current focus is on the extraordinarily complex analysis of the enormous amounts of data now being obtained from many thousands of individuals, ideally in conjunction with deep knowledge of their phenotypic characteristics, especially including their medical history.

Readily measured biomarkers of disease are powerful adjuncts to DNA sequence information. Simple blood or other tests can be developed to monitor real-time progress or failure of treatment, and many such examples already exist. Similarly, chemical, radiological, or genetic tests may be useful not only to monitor therapy but also to predict success or failure, anticipate unwanted effects of treatment, or appreciate pharmacokinetic variables that may require adjustments of dosage or choice of drugs. Such tests already play a significant role in the choice of drugs for cancer chemotherapy, and the list of drugs specifically designed to "hit" a mutated target in a specific cancer is growing. Such information is also becoming increasing useful in the choice of patients for clinical trials of specific agents—thereby reducing the time required for such trials and their cost, to say nothing of better defining the patient population who may benefit from the drug. These important subjects are discussed in detail in Chapter 7, Pharmacogenetics.

Public Policy Considerations and Criticisms of the Pharmaceutical Industry

Drugs can save lives, prolong lives, and improve the quality of people's lives. However, in a free-market economy, access to drugs is not equitable. Not surprisingly, there is tension between those who treat drugs as entitlements and those who view drugs as high-tech products of a capitalistic society. Supporters of the entitlement position argue that a constitutional right to life should guarantee access to drugs and other healthcare, and they are critical of pharmaceutical companies and others who profit from the business of making and selling drugs. Free-marketers point out that, without a profit motive, it would be difficult to generate the resources and innovation required for new drug development. Given the public interest in the pharmaceutical industry, drug development is both a scientific process and a political one in which attitudes can change quickly. Two decades ago, Merck was named as America's most admired company by *Fortune* magazine 7 years in a row—a record that still stands. In the 2015 survey of the most admired companies in the U.S., no pharmaceutical company ranked in the top 10.

Critics of the pharmaceutical industry frequently begin from the position that people (and animals) need to be protected from greedy and unscrupulous companies and scientists (Kassirer, 2005). In the absence of a government-controlled drug development enterprise, our current system relies predominantly on investor-owned pharmaceutical companies that, like other companies, have a profit motive and an obligation to shareholders. The price of prescription drugs causes great consternation among consumers, especially as many health insurers seek to control costs by choosing not to cover certain "brand-name" products (discussed later). Further, a few drugs (especially for treatment of cancer) have been introduced to the market in recent years at prices that greatly exceeded the costs of development, manufacture, and marketing of the product. Many of these products were discovered in government laboratories or in university laboratories supported by federal grants.

The U.S. is the only large country that places no controls on drug prices and where price plays no role in the drug approval process. Many U.S. drugs cost much more in the U.S. than overseas; thus, U.S. consumers subsidize drug costs for the rest of the world, and they are irritated by that fact. The example of new agents for the treatment of hepatitis C infection brings many conflicting priorities into perspective (Box 1–3).

The drug development process is long, expensive, and risky (see Figure 1–1 and Table 1–1). Consequently, drugs must be priced to recover the substantial costs of invention and development and to fund the marketing efforts needed to introduce new products to physicians and patients. Nevertheless, as U.S. healthcare spending continues to rise at an alarming pace, prescription drugs account for only about 10% of total U.S. healthcare expenditures (CDC, 2013), and a significant fraction of this drug cost is for low-priced, nonproprietary medicines. Although the increase in prices is significant in certain classes of drugs (e.g., anticancer agents), the total price of prescription drugs is growing at a slower rate than other healthcare costs. Even drastic reductions in drug prices that would

BOX 1–3 ■ The Cost of Treating Hepatitis C

Infection with hepatitis C virus (HCV) is a chronic disease afflicting millions of people. Some suffer little from this condition; many others eventually develop cirrhosis or hepatocellular carcinoma. Who should be treated? The answer is unknown. Until recently, the treatment of choice for people with genotype 1 HCV involved year-long administration of an interferon (by injection) in combination with ribavirin and a protease inhibitor. Unwanted effects of this regimen are frequent and severe (some say worse than the disease); cure rates range from 50% to 75%. A newer treatment involves an oral tablet containing a combination of sofosbuvir and ledipasvir (see Chapter 63). Treatment usually requires daily ingestion of one tablet, for 8–12 weeks; cure rates exceed 95%, and side effects are minimal.

Controversy surrounds the price of the treatment, about $1000/d. Some insurers refused to reimburse this high cost, relegating many patients to less-effective, more toxic, but less-expensive treatment. However, these third-party payers have negotiated substantial discounts of the price, based on the availability of a competing product. Is the cost exorbitant? Should insurers, rather than patients and their physicians, be making such important decisions?

Continued and excessive escalation of drug and other healthcare costs will bankrupt the healthcare system. The question of appropriate cost involves complex pharmacoeconomic considerations. What are the relative costs of the two treatment regimens? What are the savings from elimination of the serious sequelae of chronic HCV infection? How does one place value to the patient on the less-toxic and more effective and convenient regimen? What are the profit margins of the company involved? Who should make decisions about costs and choices of patients to receive various treatments? How should we consider cases (unlike that for HCV) for which the benefits are quite modest, such as when a very expensive cancer drug extends life only briefly? One astute observer (and an industry critic of many drug prices) summarized the situation as follows: "great, important problem; wrong example."

severely limit new drug invention would not lower the overall healthcare budget by more than a few percent.

Are profit margins excessive among the major pharmaceutical companies? There is no objective answer to this question. Pragmatic answers come from the markets and from company survival statistics. The U.S. free-market system provides greater rewards for particularly risky and important fields of endeavor, and many people agree that the rewards should be greater for those willing to take the risk. The pharmaceutical industry is clearly one of the more risky:

- The costs to bring products to market are enormous.
- The success rate is low (accounting for much of the cost).
- Accounting for the long development time, effective patent protection for marketing a new drug is only about a decade (see Intellectual Property and Patents), requiring every company to completely reinvent itself on roughly a 10-year cycle.
- Regulation is stringent.
- Product liability is great.
- Competition is fierce.
- With mergers and acquisitions, the number of companies in the pharmaceutical world is shrinking.

Many feel that drug prices should be driven more by their therapeutic impact and their medical need, rather than by simpler free-market considerations; there is movement in this direction. Difficulties involve estimation or measurement of value, and there are many elements in this equation (Schnipper et al., 2015). There is no well-accepted approach to answer the question of value.

Who Pays?

The cost of prescription drugs is borne by consumers ("out of pocket"), private insurers, and public insurance programs such as Medicare, Medicaid, and the SCHIP. Recent initiatives by major retailers and mail-order pharmacies run by private insurers to offer consumer incentives for purchase of generic drugs have helped to contain the portion of household expenses spent on pharmaceuticals; however, more than one-third of total retail drug costs in the U.S. are paid with public funds—tax dollars.

Healthcare in the U.S. is more expensive than everywhere else, but it is not, on average, demonstrably better than everywhere else. One way in which the U.S. system falls short is with regard to healthcare access. Although the Patient Protection and Affordable Care Act of 2010 has reduced the percentage of Americans without health insurance to a historic low, practical solutions to the challenge of providing healthcare for all who need it must recognize the importance of incentivizing innovation.

Intellectual Property and Patents

Drug invention produces intellectual property eligible for patent protection, protection that is enormously important for innovation. As noted in 1859 by Abraham Lincoln, the only U.S. president to ever hold a patent (for a device to lift boats over shoals), by giving the inventor exclusive use of his or her invention for a limited time, the patent system "added the fuel of interest to the fire of genius in the discovery and production of useful things (Lincoln, 1859)." The U.S. patent protection system provides protection for 20 years from the time the patent is filed. During this period, the patent owner has exclusive rights to market and sell the drug. When the patent expires, equivalent nonproprietary products can come on the market; a generic product must be therapeutically equivalent to the original, contain equal amounts of the same active chemical ingredient, and achieve equal concentrations in blood when administered by the same routes. These generic preparations are sold much more cheaply than the original drug and without the huge development costs borne by the original patent holder.

The long time course of drug development, usually more than 10 years (see Figure 1–1), reduces the time during which patent protection functions as intended. The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417, informally called the Hatch-Waxman Act) permits a patent holder to apply for extension of a patent term to compensate for delays in marketing caused by FDA approval processes; nonetheless, the average new drug brought to market now enjoys only about 10–12 years of patent protection. Some argue that patent protection for drugs should be shortened, so that earlier generic competition will lower healthcare costs. The counterargument is that new drugs would have to bear even higher prices to provide adequate compensation to companies during a shorter period of protected time. If that is true, lengthening patent protection would actually permit lower prices. Recall that patent protection is worth little if a superior competitive product is invented and brought to market.

Bayh-Dole Act

The Bayh-Dole Act (35 U.S.C. § 200) of 1980 created strong incentives for federally funded scientists at academic medical centers to approach drug invention with an entrepreneurial spirit. The act transferred intellectual property rights to the researchers and their respective institutions (rather than to the government) to encourage partnerships with industry that would bring new products to market for the public's benefit. While the need to protect intellectual property is generally accepted, this encouragement of public-private research collaborations has given rise to concerns about conflicts of interest by scientists and universities (Kaiser, 2009).

Biosimilars

As noted previously, the path to approval of a chemically synthesized small molecule that is identical to an approved compound whose patent protection has expired is relatively straightforward. The same is not true for large molecules (usually proteins), which are generally derived from a living organism (e.g., eukaryotic cell or bacterial culture). Covalent modification of proteins (e.g., glycosylation) or conformational differences may influence pharmacokinetics, pharmacodynamics, immunogenicity, or other properties, and demonstration of therapeutic equivalence may be a complex process.

The Biologics Price Competition and Innovation Act was enacted as part of the Patient Protection and Affordable Care Act in 2010. The intent was to implement an abbreviated licensure pathway for certain "similar" biological products. *Biosimilarity* is defined to mean "that the biological product is highly similar to a reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." In general, an application for licensure of a biosimilar must provide satisfactory data from analytical studies, animal studies, and a clinical study or studies. The interpretation of this language has involved seemingly endless discussion, and hard-and-fast rules seem unlikely.

Drug Promotion

In an ideal world, physicians would learn all they need to know about drugs from the medical literature, and good drugs would thereby sell themselves. Instead, we have print advertising and visits from salespeople directed at physicians and extensive direct-to-consumer advertising aimed at the public (in print, on the radio, and especially on television). There are roughly 80,000 pharmaceutical sales representatives in the U.S. who target about 10 times that number of physicians. This figure is down from about 100,000 in 2010, and the decline is likely related to increased attention to real and actual conflicting interests caused by their practices. It has been noted that college cheerleading squads are attractive sources for recruitment of this sales force. The amount spent on promotion of drugs approximates or perhaps even exceeds that spent on research and development. Pharmaceutical companies have been especially vulnerable to criticism for some of their marketing practices.

Promotional materials used by pharmaceutical companies cannot deviate from information contained in the package insert. In addition, there must be an acceptable balance between presentation of therapeutic claims for a product and discussion of unwanted effects. Nevertheless, direct-to-consumer advertising of prescription drugs remains controversial and is permitted only in the U.S. and New Zealand. Canada allows a modified form of advertising in which either the product or the indication can be mentioned, but not both. Physicians frequently succumb with misgivings to patients' advertising-driven requests for specific medications.

The counterargument is that patients are educated by such marketing efforts and in many cases will then seek medical care, especially for conditions (e.g., depression) that they may have been denying (Avery et al., 2012).

The major criticism of drug marketing involves some of the unsavory approaches used to influence physician behavior. Gifts of value (e.g., sports tickets) are now forbidden, but dinners where drug-prescribing information is presented by non-sales representatives are widespread. Large numbers of physicians are paid as "consultants" to make presentations in such settings. The acceptance of any gift, no matter how small, from a drug company by a physician is now forbidden at many academic medical centers and by law in several states. In 2009, the board of directors of PhRMA adopted an enhanced Code on Interactions With Healthcare Professionals that prohibits the distribution of noneducational items, prohibits company sales representatives from providing restaurant meals to healthcare professionals (although exceptions are granted when a third-party speaker makes the presentation), and requires companies to ensure that their representatives are trained about laws and regulations that govern interactions with healthcare professionals.

Concerns About Global Injustice

Because development of new drugs is so expensive, private-sector investment in pharmaceutical innovation has focused on products that will have lucrative markets in wealthy countries such as the U.S., which combines patent protection with a free-market economy. Accordingly, there is concern about the degree to which U.S. and European patent protection laws have restricted access to potentially lifesaving drugs in developing countries.

To lower costs, pharmaceutical companies increasingly test their experimental drugs outside the U.S. and the E.U., in developing countries where there is less regulation and easier access to large numbers of patients. According to the U.S. DHHS, there has been a 2000% increase in foreign trials of U.S. drugs over the past 25 years. When these drugs are successful in obtaining marketing approval, consumers in the countries where the trials were conducted often cannot afford them. Some ethicists have argued that this practice violates the justice principle articulated in the Belmont Report (DHHS, 1979, p10), which states that "research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research." A counterargument is that the conduct of trials in developing nations also frequently brings needed medical attention to underserved populations. This is another controversial issue.

Product Liability

Product liability laws are intended to protect consumers from defective products. Pharmaceutical companies can be sued for faulty design or manufacturing, deceptive promotional practices, violation of regulatory requirements, or failure to warn consumers of known risks. So-called failure-to-warn claims can be made against drug makers even when the product is approved by the FDA. With greater frequency, courts are finding companies that market prescription drugs directly to consumers responsible when these advertisements fail to provide an adequate warning of potential adverse effects.

Although injured patients are entitled to pursue legal remedies, the negative effects of product liability lawsuits against pharmaceutical companies may be considerable. First, fear of liability may cause pharmaceutical companies to be overly cautious about testing, thereby delaying access to the drug. Second, the cost of drugs increases for consumers when pharmaceutical companies increase the length and number of trials they perform to identify even the smallest risks and when regulatory agencies increase the number or intensity of regulatory reviews. Third, excessive liability costs create disincentives for development of so-called orphan drugs, pharmaceuticals that benefit a small number of patients. Should pharmaceutical companies be liable for failure to warn when all of the rules were followed and the product was approved by the FDA but the unwanted effect was not detected because of its rarity or another confounding factor? The only way to find "all" of the unwanted effects that a drug may have is to market it—to conduct a phase IV "clinical trial" or observational study. This basic friction between risk to patients and the financial risk of drug development does not seem likely to be resolved except on a case-by-case basis, in the courts.

The U.S. Supreme Court added further fuel to these fiery issues in 2009 in the case *Wyeth v. Levine*. A patient (Levine) suffered gangrene of an arm following inadvertent arterial administration of the antinausea drug promethazine. She subsequently lost her hand. The healthcare provider had intended to administer the drug by so-called intravenous push. The FDA-approved label for the drug *warned against*, but did not prohibit, administration by intravenous push. The state court and then the U.S. Supreme Court held both the healthcare provider *and the company* liable for damages. Specifically, the Vermont court found that Wyeth had inadequately labeled the drug. This means that FDA approval of the label does not protect a company from liability or prevent individual states from imposing regulations more stringent than those required by the federal government.

"Me Too" Versus True Innovation: The Pace of New Drug Development

Me-too drug is a term used to describe a pharmaceutical that is usually structurally similar to a drug already on the market. Other names used are *derivative medications*, *molecular modifications*, and *follow-up drugs*. In some cases, a me-too drug is a different molecule developed deliberately by a competitor company to take market share from the company with existing drugs on the market. When the market for a class of drugs is especially large, several companies can share the market and make a profit. Other me-too drugs result coincidentally from numerous companies developing products simultaneously without knowing which drugs will be approved for sale (Box 1–4).

There are valid criticisms of me-too drugs. First, an excessive emphasis on profit may stifle true innovation. Of the 487 drugs approved by the FDA between 1998 and 2003, only 67 (14%) were considered by the FDA to be NMEs. Between 1998 and 2011, on average only 24 NMEs were approved by the FDA's CDER. Second, some me-too drugs are more expensive than the older versions they seek to replace, increasing the costs of healthcare without corresponding benefit to patients. Nevertheless, for some patients, me-too drugs may have better efficacy or fewer side effects or promote compliance with the treatment regimen. For example, the me-too that can be taken once a day rather than more frequently is convenient and promotes compliance. Some me-too drugs add great value from a business and medical point of view. Atorvastatin was the seventh statin to be introduced to market; it subsequently became the best-selling drug in the world.

Critics argue that pharmaceutical companies are not innovative and do not take risks, and, further, that medical progress is actually slowed by their excessive concentration on me-too products. Figure 1–2 summarizes a few of the facts behind this and other arguments. Clearly, only a modest number of NMEs, about two dozen a year, achieved FDA approval in the years 1980 to 2011, with the exception of the several-year spike in approvals following the introduction of PDUFA. Yet, from 1980 to 2010, the industry's annual investment in research and development grew from

BOX 1–4 ■ A Not-So-New Drug

Some me-too drugs are only slightly altered formulations of a company's own drug, packaged and promoted as if really offering something new. An example is the heartburn medication esomeprazole, marketed by the same company that makes omeprazole. Omeprazole is a mixture of two stereoisomers; esomeprazole contains only one of the isomers and is eliminated less rapidly. Development of esomeprazole created a new period of market exclusivity, although generic versions of omeprazole are marketed, as are branded congeners of omeprazole/esomeprazole. Both omeprazole and esomeprazole are now available over the counter—narrowing the previous price difference.

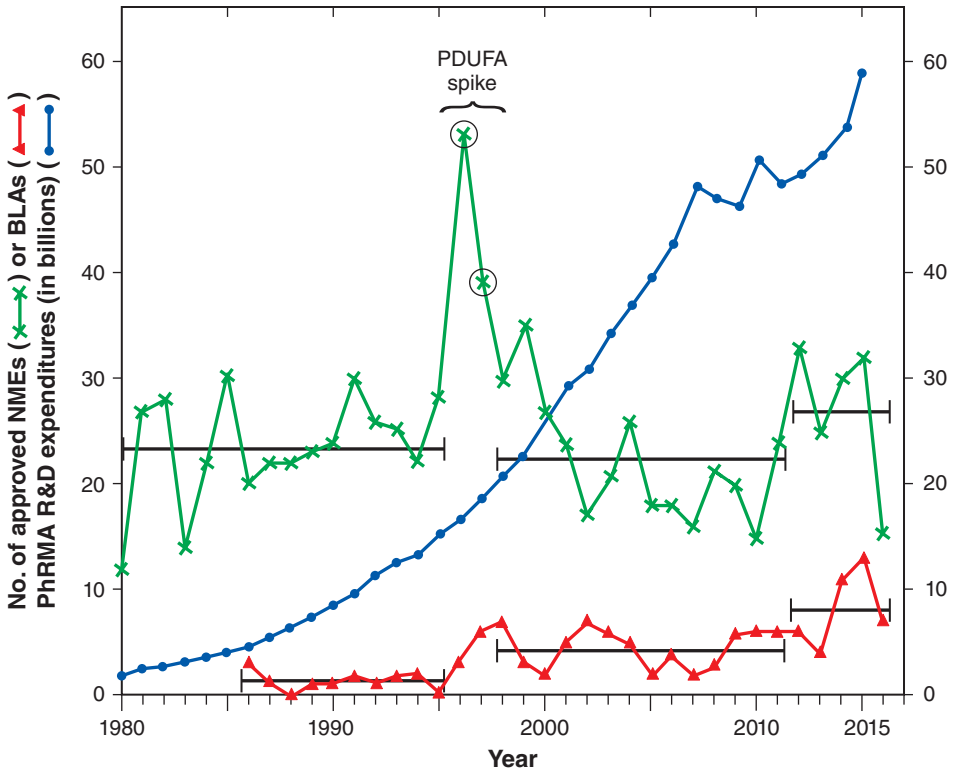

Figure 1–2 *The cost of drug invention is rising. Is productivity?* Each horizontal black line shows the average annual number of NMEs or BLAs for the time period bracketed by the line's length.

$2 billion to $50 billion. This disconnect between research and development investment and new drugs approved occurred at a time when combinatorial chemistry was blooming, the human genome was being sequenced, highly automated techniques of screening were being developed, and new techniques of molecular biology and genetics were offering novel insights into the pathophysiology of human disease.

In recent years, there has been a modest increase in approval of NMEs (inhibitors of a number of protein kinases) and new biologics (numerous therapeutic antibodies) (see Figure 1–2). A continued increase in productivity will be needed to sustain today's pharmaceutical companies as they face waves of patent expirations. There are strong arguments that development of much more targeted, individualized drugs, based on a new generation of molecular diagnostic techniques and improved understanding of disease in individual patients, will improve both medical care and the survival of pharmaceutical companies.

Finally, many of the advances in genetics and molecular biology are still new, particularly when measured in the time frame required for drug development. One can hope that modern molecular medicine will sustain the development of more efficacious and more specific pharmacological treatments for an ever-wider spectrum of human diseases.

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