

# CRS Report for Congress

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## **Pharmaceutical Research and Development: A Description and Analysis of the Process**

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# Pharmaceutical Research and Development: A Description and Analysis of the Process

## Summary

A central element of the debate about inclusion of prescription drug benefits in Medicare is the price of prescription drugs. A key issue in the debate concerns the relationship between those prices and the pharmaceutical research and development (R&D) costs. While this report will not analyze that relationship directly, it does present a description and assessment of the pharmaceutical R&D (drug development) process and the factors that affect costs. Such an analysis should be useful in addressing questions about the cost of pharmaceutical R&D and the dependence of prescription drug prices in the United States on those costs.

Pharmaceutical R&D (drug development) consists of several stages. It begins with drug discovery followed by preclinical drug development where thousands of candidate chemicals may be screened for attractive therapeutic, pharmacological, and toxicity properties. Successful candidates — usually 5 or fewer from an original pool that may total 10,000 — are then subjected to three stages of clinical trials testing the drugs' effectiveness and side effects. If a drug emerges from the trials showing a significant therapeutic benefit, it is submitted to the Food and Drug Administration for marketing approval. If approved, post-marketing surveillance ensues looking for possible safety concerns that did not emerge in the earlier trials.

The entire drug development process typically takes nearly 15 years. The largest share of that time is devoted to the three stages of clinical trials. Although there is no firm figure for the cost of drug development, estimates have run as high as \$500 million for the costs associated with a typical drug. While these costs cannot be stated with any real precision, the true cost is still probably high, and the major share of those costs is for clinical trials.

Recent advances in molecular biology making use of genetic data developed in the human genome project offer the promise of significantly shortening both drug development and clinical trial time, although it may be several years before these goals are routinely realized. Any significant shortening of the development time could reduce pharmaceutical R&D costs and, possibly, prescription drug prices. Another factor in the cost equation is the contribution of basic biomedical research funded by the National Institutes of Health. Such research is very important for drug development, and benefits the pharmaceutical industry by reducing its R&D costs.

There are several issues about pharmaceutical R&D that Congress may decide to monitor closely. Two, which are within the scope of this report, concern federal biomedical R&D funding and clinical trial practices. With respect to the first, a particular concern is the possibility of unnecessary overlap in research sponsored by both NIH and the industry as the latter strives to incorporate more of the promise of molecular biology into the pharmaceutical R&D process. With respect to clinical trial practice, of specific concern are human subject protection and the potential for conflict of interest on the part of academic researchers taking part in clinical trials.

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# Pharmaceutical Research and Development: A Description and Analysis of the Process

## Introduction

Perhaps the central issue in the debate about inclusion of prescription drug benefits in Medicare has been whether such action would lead to some type of price controls for these drugs.<sup>1</sup> A key element of that debate is the relationship between prescription drug prices and the research and development (R&D) activities of the pharmaceutical industry.

In 2000, the world-wide, research-based pharmaceutical industry spent an estimated \$26.4 billion on R&D including \$22.4 billion in the United States.<sup>2</sup> The U.S. and world-wide totals were up by about \$2.4 billion, or 10%, from 1999. For 2000, these R&D expenditures constituted an estimated 20% of the sales of these companies. It is the contention of the industry that current prices are required if that R&D is to continue at a level sufficient to develop drugs to attack many of the diseases now afflicting humankind. Critics, however, argue that those prices are higher than can be justified by R&D costs.

The purpose of this report is to help the reader understand the pharmaceutical R&D process as part of the knowledge needed to evaluate the debate about drug pricing. In addition, however, the pharmaceutical R&D process and future prospects raise a number of issues on their own. This report provides a description of that process and analyzes a number of those key issues. The steps of the research process — drug discovery, preclinical testing, clinical trials, and post approval monitoring — are described. In addition, various factors affecting the duration and costs of the process are discussed, including the possible consequences of recent advances in biomedical research. Finally, an analysis is presented of topics pertinent to the R&D process that may be of interest to Congress.

Although the report discusses pharmaceutical R&D costs, it does not present an analysis of the validity of various cost estimates. Those and other areas related to

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<sup>1</sup>For a discussion of these issues see Congressional Research Service, *Medicare: Selected Prescription Drug Proposals*, by Jennifer O’Sullivan, RL30584, Updated September 14, 2000.

<sup>2</sup>Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile – 2000* (PhRMA, Washington, DC, 2000), 20.  
<http://www.phrma.org/publications/publications/profile00/>

pharmaceuticals R&D and prescription drugs, including patent protection, regulation, and advertising, are now or will be covered in other CRS studies.<sup>3</sup>

## Background

A description of the pharmaceutical R&D process requires a brief review of the relevant biology, both to help the reader understand the origins of most human disease and how most drugs work in combating diseases. The section begins with a brief discussion of the basic biological mechanisms of living systems and how disease attacks those systems. It next presents a short discussion of the biological processes by which pharmaceuticals work in combating disease.

### Biological Basis of Disease

Of the different chemical compounds that are essential for human organisms, proteins play crucial roles in most human biological functions and provide much structural support. Proteins provide structural support for the body as critical components of ligaments, tendons, and skin. Enzymes are proteins that accelerate the essential chemical reactions in the cell. Antibodies are proteins that protect cells from attack by foreign substances called antigens. Hormones that regulate cell metabolism are proteins.<sup>4</sup> Within the membrane (wall) of the cell, proteins act as receptors, attaching to and transporting essential chemicals into the interior of the cell. Proteins perform many other functions as well.

The instructions contained in the genetic code are translated to control of cellular behavior through the synthesis of proteins. The genes contained in the DNA molecule code instructions for the chains of amino acids which are the building blocks of proteins. Furthermore, this gene expression is itself regulated by other proteins. Proteins are large molecules, containing hundreds to thousands of atoms, and are arranged in very complex shapes. For those proteins responsible for controlling functions — enzymes, receptors, hormones, etc. — both the chemical structure and the shape determine how they react with other chemicals.

Because proteins are so important to the functioning of living systems, they are naturally almost always involved when something goes wrong. In most cases the

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<sup>3</sup>See for example, Congressional Research Service, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Extension Act of 1984*, by Wendy Schacht and John R. Thomas, RL30756, December 5, 1999; Congressional Research Service, *Prescription Drugs: Factors Influencing their Pricing*, by David Cantor, 96-296, Updated Feb. 3, 1998; Congressional Research Service, *Food and Drug Administration Modernization Act of 1997*, by Richard Rowberg, et. al., 98-263, March 13, 1998; and Congressional Research Service, *Food and Drug Administration: Selected Funding and Policy Issues*, by Donna Vogt, 95-422, Updated February 27, 2001.

<sup>4</sup>Not all hormones are proteins. Another common class of hormones are steroids such as testosterone, vitamin D, and cholesterol.

problems occur with proteins that are either enzymes, receptors, or hormones.<sup>5</sup> Many cancers result when proteins that control the rate at which cells divide no longer function properly, and cells begin to multiply in an uncontrolled manner. Infections can damage a living organism when bacteria or viruses produce toxins that inhibit protein synthesis, resulting in the death of cells. These microbes can also cause damage by invading and multiplying within cells and tissues. Fever and inflammation result through the action of the body's immune system attacking the intruders. In the case of AIDS, proteins on the human immunodeficiency virus (HIV) bind to receptor proteins on cells of the immune system. The virus is then able to invade those cells, reproduce, and eventually destroy the cells. As a result, the immune system weakens and is unable to stop other microbial invasions called opportunistic infections.

Other diseases result from problems with hormone production or utilization. Diabetes I occurs when the body does not produce the hormone insulin while diabetes II occurs when insulin production is normal but the body cannot use it. In the cardiovascular system, proteins called low density lipoprotein (LDL) deposit cholesterol stored in fat cells on body tissue including the insides of blood vessels. High density lipoprotein (HDL), on the other hand, carries the cholesterol to the liver for recycling. Therefore, if the ratio of LDL to HDL is too high, the individual is at risk for heart disease.

Identifying and understanding protein behavior, therefore, are primary objectives of research into disease and its causes. Because of the connection between genes and proteins, it is also clear that genes play an important role in disease mechanisms. Indeed protein behavior that leads to disease can often be attributed to genetic mutations that result in creation of proteins that do not behave normally or of failure to create needed proteins. For example, cystic fibrosis results from a genetic mutation that prevents the formation of proteins allowing chloride to pass through cell walls. Over 4000 diseases have been identified as having a genetic origin,<sup>6</sup> although many of those are rare. Some are the result of single gene mutations while others result from a combination of multiple gene mutations and other factors. Because of this gene-protein linkage, genetics has been and continues to be the target of research in understanding disease and its origins.

## Basics of Pharmaceuticals

Given the role of proteins in disease it is natural that the focus of most drug therapy is to inhibit protein activity that causes physiological harm to humans or to stimulate protein activity that is needed by the body but is lacking.<sup>7</sup> For example, aspirin works for pain mitigation by inhibiting the action of a protein that, when stimulated, is responsible for producing a chemical that results in pain. Aspirin

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<sup>5</sup>For a general discussion of the role of proteins in disease, see Susan Aldridge, *Magic Molecules: How Drugs Work* (Cambridge: Cambridge University Press, 1998).

<sup>6</sup>Eric S. Grace, *Biotechnology Unzipped: Promises and Realities* (Washington: Joseph Henry Press, 1997), 62.

<sup>7</sup>See Aldridge, *Magic Molecules*, 6-11, 73 and Jurgen Drews, *In Quest of Tomorrow's Medicines* (New York: Springer, 1998), 118-121.

contains chemicals that bind with that protein, preventing it from acting. As a stimulant for protein activity, drugs can bind with receptors, causing the cells on which they are located to carry out desired biochemical activity. For example, when insulin binds with its target receptor, the cells act to maintain steady levels of glucose in the blood stream. Many cancer drugs work by actions that inhibit proteins responsible for maintaining multiplication of cancerous cells, resulting in the death of those cells (as well as other rapidly dividing cells). Antibiotics kill bacteria by inactivating enzymes on bacterial cell membranes, causing them to stop forming, or by halting the synthesis of proteins needed to sustain the microbe's life.

While the basis of most pharmaceutical action sounds straightforward, implementing such action is usually very difficult. Determining targets for drugs can be a daunting, costly task as has been repeatedly demonstrated from the history of biomedical research. For example, the research effort to discover the proteins responsible for cancerous cell growth and how they work has consumed many billions of dollars and several decades, and complete understanding still appears a long way off. Furthermore, once a target is determined, discovering a chemical that will bind with that target protein and either inhibit or aid its actions as need be is not assured.<sup>8</sup> As stated above, proteins have very complex shapes that determine how other molecules bind with them, and even if one can discover such molecules, the drug still may not work in humans. Human biological processes on the molecular level are extremely complicated and research efforts to understand those processes and bring about chemical therapies for disease are substantial.

Just how is that research carried out? How are the fundamentals outlined above applied to bring about the development of prescription drugs? The next section provides a description of the pharmaceutical R&D process as it is typically performed. Reference is made wherever appropriate to the biological basis of disease and pharmaceuticals just presented.

## The Research Process

This section discusses the pharmaceutical research process. The section begins with a brief overview of the entire process. It then describes in more detail the basic research phase of pharmaceutical research, drug discovery, followed by a discussion of preclinical research. A description of the clinical trial phase is given next followed by a review of the post-approval process. A brief survey of the history of pharmaceutical R&D is given in Appendix A.

### Overview

Drug research and development begins with the drug discovery phase. Typically, at this stage, chemical compounds — either naturally occurring (called biologics) or synthetic — are investigated in laboratory settings for their potential to bind to and

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<sup>8</sup> In the case of aspirin and penicillin, the biological basis of the drugs' actions were not discovered until many years after the drugs themselves were discovered.

modify target molecules. Once promising candidates are identified, preclinical testing begins. In this stage, actual drug development begins and pharmacological studies are carried out. Basically that research focuses on how the drug candidates react when delivered to the body.

If promising candidates emerge from these first two stages, they enter the most arduous and time-consuming portion of the R&D process, clinical trials. There are three stages to clinical trials — called phase I, phase II, and phase III — that a candidate drug must pass through before it can be considered for market approval. In phase I, the safety of the candidate drug is tested on healthy volunteers. Once safety screening is complete, testing begins on a population of patients who have the disease. Then, phase II trials are held to establish the parameters (end points) for the quantitative measurement of the effectiveness of the drug. Phase III trials are basically a large-scale version of phase II trials. In phase III, however, the focus is on obtaining quantitative measurements of the effectiveness of the drug, based on the end points determined in the phase II trials, and on monitoring for any important side effects.

If the results of the phase III trials provide a clear indication of the candidate drug's effectiveness and that any side effects can be reasonably managed, it is submitted to the Food and Drug Administration for approval to market. During that process, it is possible that FDA may require additional phase III trials. If approval is granted, post-marketing surveillance is carried out to monitor the drug for additional safety concerns that may not have appeared during the preapproval clinical trials. Additional trials — phase IV — may also be required at this point.

Each of these steps is complex and uncertain, and each requires a substantial commitment of time and resources. To gain some insight into those characteristics, each step will now be described in more detail.

## Drug Discovery

Drug discovery usually begins with research to identify potential drug targets. Targets are biochemical compounds in the body — usually proteins, as noted above — whose action or absence of actions results in a diseased condition.<sup>9</sup> In some cases, drugs have been discovered without researchers knowing an underlying cause of the disease. Aspirin was discovered long before the mechanism by which it works was determined. Much more often, however, particularly in recent years, identification of drug targets has launched the search for therapies. Usually the search is aided by new knowledge of biological processes and disease mechanisms resulting from basic

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<sup>9</sup>Most illness and death from illness is a result of viral or bacterial infection. Proteins are still the target of antibiotic and antiviral drugs, although they belong to the invading microbes and not the host. Blocking bacterial enzymes or inhibiting protein synthesis are the principal objectives of antibiotics. Drugs that work with viruses usually bind on viral enzymes, inhibiting their action. Vaccines against infectious diseases work by presenting an antigen to the host's immune system. Antigen proteins, carried on the surface of a virus, stimulate the immune system when a virus enters (Aldridge, *Magic Molecules*, 72-82).



biomedical research, much of which is funded by the National Institutes of Health (NIH).

Diseases often have multiple biochemical causes or factors. Discovery of a single factor in such a case may not lead to a useful drug target. As noted above, the complexity of most diseases means that identification of targets is generally quite difficult. It is estimated that thousands of potential targets exist in the body.<sup>10</sup> By 1996, however, a survey of drug targets on which current drug therapy was based found that only about 500 targets were being used, 45% of which were receptors and 28% of which were enzymes.<sup>11</sup> The remaining 27% consist of a variety of targets including hormones, DNA molecules, and cell nuclei receptors, or are unknown.

The actual process of drug discovery is characterized by a search for molecules that can bind to targets and result in an action that produces a therapeutic result. Until the last few decades, this search was largely a trial and error process.<sup>12</sup> Pharmaceutical companies would develop libraries of thousands of molecules over the years from a variety of sources.<sup>13</sup> When a promising target was identified, researchers would test molecules from these libraries, largely by trial and error or random screening, to look for potential therapeutic activity. Many different natural and synthetic compounds — thousands to tens of thousands — were tried in laboratory experiments, often using animals, to see whether they showed therapeutic promise. Often, the biochemical basis for any therapeutic effect was not understood, and at times a substance being screened would be found to treat an ailment different from the one for which the screening was intended.<sup>14</sup> In addition to being time-consuming and resource intensive, discoveries obtained in this fashion usually did not yield findings that could be generalized to aid in the search for therapies to other diseases. Consequently, while this method of drug discovery has resulted in many new drugs over the years, the industry has put major efforts into development of more rational approaches.

In recent years search methods have become more systematic.<sup>15</sup> Using a technique known as combinatorial chemistry, literally thousands of candidate drug compounds can be produced in a systematic and automatic fashion. In this situation, a candidate molecule is modified, atom-by-atom, producing a large number of similar molecules to be tested for therapeutic action. Testing itself is done using automated

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<sup>10</sup>Aldridge, *Magic Molecules*, 257.

<sup>11</sup>Jurgen Drews, "Drug Discovery: A Historical Perspective," *Science* 287 (2000), 1961.

<sup>12</sup>Drews, *In Quest of Tomorrow's Medicine*, 121.

<sup>13</sup>While most of these molecules are produced synthetically, a large fraction of prescription drugs on the market comes from natural sources. Of the 520 drugs approved between 1983 and 1994, 39% were either natural products or derivatives of natural products (Alan Harvey, "Strategies for discovering drugs from previously unexplored natural products," *Drug Discovery Today*, 5 (July 2000), 294).

<sup>14</sup>National Research Council, "U.S. Industry in 2000: Studies in Competitive Performance," *Pharmaceuticals and Biotechnology*, (National Academy Press, Washington, DC, 1999) 368.

<sup>15</sup>Drews, "Drug Discovery: A Historical Perspective," 1962.

methods including monitoring the interactions using a high-throughput screening process. Results which modify the targets are explored further giving rise to more information about those compounds. The use of combinational chemistry expanded rapidly in the 1990s, and a huge library of potential drugs exists in those companies employing this technique.<sup>16</sup>

Advances in molecular biology (see box) are also having a profound effect on drug discovery. First, they are leading to a substantial increase in understanding the origin and causes of diseases. Application of molecular biology developments is changing the way researchers identify drug targets. More about this application will be discussed below. Second, biotechnology (see box) has been used to bring about dramatic increases in the production of certain drugs (e.g., insulin) whose efficacy was already established. Third, new results from molecular biology research are being used to enhance the search for other drugs.<sup>17</sup> As a research tool, genetic engineering (see box) is used to produce “pure” screens on which to test new drug candidates.<sup>18</sup> Therefore, rather than relying on a screen that may contain the target in question among others, the receptor can be synthesized and made to exist alone, allowing a more rational and effective test of the drug.<sup>19</sup> Recent developments in biotechnology are only just beginning to make major contributions to drug discovery, however, and they promise to revolutionize the entire pharmaceutical R&D process.

*Molecular Biology* – The study of the properties and functions of living organisms at the molecular level. The objective is to understand the behavior of the molecules that make up an organism’s cells and the interactions between those molecules. The principal foci of molecular biology research are the molecular structure of genes — in particular the DNA molecule — and the structure and behavior of protein molecules.

*Biotechnology* – The technique of using living cells to make useful products and provide services. Modern biotechnology involves the manipulation of the molecules making up cells, such as DNA and RNA.

*Genetic Engineering* – A type of biotechnology that involves manipulation of genetic material to produce desired types of living organisms or to correct genetic defects.

## Preclinical Testing

Once promising drug candidates have been identified, they enter the preclinical research stage. The candidates undergo laboratory and animal testing focusing on the

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<sup>16</sup>Robert Service, “Winning combination,” *Technology Review*, 101 (1998), 34-42.

<sup>17</sup>National Research Council, “U.S. Industry in 2000: Studies in Competitive Performance,” 378.

<sup>18</sup>Screens are small samples of chemical or biological substances that contain drug target molecules. They are used for initial testing of drug candidates to look for those candidates that will bind with the target.

<sup>19</sup>National Research Council, “U.S. Industry in 2000,” 381.

pharmacological aspects of drug development. Of the about 5,000 to 10,000 drug candidates screened during the drug discovery stage, about 250 will typically make it to the preclinical research stage.<sup>20</sup> During this phase, the pharmacological concerns of toxicity, bioavailability,<sup>21</sup> and efficacy are investigated. In addition, at this point, an investigational new drug (IND) application is filed with the Food and Drug Administration (FDA), patents are applied for, and efforts are started to develop economic and quality manufacturing processes.<sup>22</sup> Safety testing takes place in animals that are administered ever increasing doses to look for onset of toxicity. Also, a key feature of this stage is to determine the best method of delivery (e.g., oral, intravenous, etc.). A drug with a low bioavailability — at or near zero — either must have its dosage increased when administered orally or it must be administered in some other way. Other tests include determining a drug candidate's shelf lifetime and shipping durability.

The first step in preclinical pharmacological testing is to determine toxicity, including the relationship between dosage and toxicity, how those effects vary over time, the organs affected, and the reversibility of any effects.<sup>23</sup> To determine how the effects change over time or whether there are long-term toxic effects, extended tests are performed. They usually last more than a year and attempt to determine a number of factors in addition to a cataloging of any risks of long-term use. Included are tests to determine dosage range, maximum dosage for no side effects, and largest tolerable dosage. In parallel, carcinogenicity studies, involving various dosage levels and lasting up to two years, are carried out. Other conditions studied include local side effects, allergenic reactions, and effects on reproduction.

During the safety testing, animals are used for studies of toxicity including chronic toxicity.<sup>24</sup> The drug's cancer-causing potential is also investigated by examining how it may damage the animal's DNA. Pregnant animals are used to look at the drug's effects on pregnancy. Animal testing is opposed by some, however, and other methods are being sought, including the use of tissue cultures, bacteria cells, and computer models. Many of these methods are now used for preliminary screening to reduce the number of animals used in safety testing.

Drug delivery is also an important objective of preclinical research. This stage involves the study of how the drug is absorbed, distributed, metabolized, and excreted by the body. Such studies are carried out on animals. In order to maximize the

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<sup>20</sup>*Pharmaceutical Industry Profile – 2000*, 32.

<sup>21</sup>Bioavailability is a measure of drug's ability to move through and remain in the human body and reach the bloodstream and the drug target with a sufficient dose for therapeutic action. For a drug taken by mouth, a high bioavailability — at or near one — means that it was not metabolized by the liver and that it penetrated the walls of the small intestine to the blood stream before being excreted (Aldridge, *Magic Molecules*, 11-12).

<sup>22</sup>An investigational new drug (IND) is a drug candidate undergoing clinical investigation or an approved drug being investigated for a new indication (use). FDA may permit an IND to be used for seriously ill patients who are not part of ongoing clinical trials.

<sup>23</sup>Drews, *In Quest of Tomorrow's Medicine*, 129-130.

<sup>24</sup>Aldridge, *Magic Molecules*, 43-44.

amount of the drug that reaches the drug target, it is necessary to develop delivery systems that minimize the absorption of the drug by healthy tissue before it can reach the target.<sup>25</sup> For example, many drugs that are proteins would be digested rapidly by the stomach and small intestine. Enzymes in the liver can deactivate many drugs if they circulate in the blood stream. If, as a result of such actions, a drug candidate will not work if taken orally, the major alternative at present is needle injection. Because injections cause discomfort and can be difficult to administer, much pharmaceutical R&D is directed at ways to deliver drugs to avoid needle injections. The dosage level of drugs must also be controlled so that they are effective but not toxic. In addition, timing of drug delivery may be important because of disease rhythms and natural body cycles, and to minimize toxic effects.

The final objective of preclinical research is the development of manufacturing methods.<sup>26</sup> Most often production is done by synthetic chemistry, but the use of genetic engineering (recombinant DNA) is growing. Other methods include fermentation<sup>27</sup> and extraction from natural sources (primarily plants). Once a method is chosen, production is scaled up to levels needed for clinical trials.

## Clinical Trials

Of the approximately 250 drug candidates that enter the preclinical research stage for a typical drug development project, about five will emerge as INDs to be tested in the clinical trial stage. Clinical trials, which constitute the most time-consuming and costly portion of drug development, consist of three phases, each more complex than the preceding. Before clinical trials can begin, the sponsoring pharmaceutical company must have approval from FDA about trial protocols (see below).

**Description.** Phase I clinical trials are designed to test drug safety; in particular to determine maximum safe dose. Small, single doses are used at first, with the dosage level increasing until side effects are observed. Concentrations of the drug in the blood are then measured. These tests are followed with multiple dose tests, and a range of concentrations that do not produce unacceptable side effects is determined. Typically, a phase I trial will include 10 to 100 participants, last about 1.5 years and cost about \$10 million.<sup>28</sup> Participants are usually healthy, although if very serious side effects are a possibility, the tests may be made on the targeted patient group.

The purpose of phase II trials is to determine the parameters for the final test (phase III trials). These parameters, among others, are the class (e.g., age, gender)

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<sup>25</sup> National Institute of General Medical Sciences, National Institutes of Health, *Medicines by Design: The Biological Revolution in Pharmacology*, NIH Report No. 93-474, September 1993, 29-30 [[http://www.nigms.nih.gov/news/science\\_ed/medbydes.html](http://www.nigms.nih.gov/news/science_ed/medbydes.html)]

<sup>26</sup> Aldridge, *Magic Molecules*, 41-42.

<sup>27</sup> Fermentation — a biotechnology process — is used to produce vast quantities of certain bacteria that, in turn, are used to produce many antibiotics and other drugs such as insulin.

<sup>28</sup> Justin A. Zivan, "Understanding Clinical Trials," *Scientific American*, 282 (April 2000), 71.

and condition of the patients to include in the trial, what end points to measure, and what constitutes an effective dose and duration of treatment. End points are those conditions that yield an unambiguous indication of the drug's success or failure. To test a drug's effectiveness often it is necessary to look for surrogate markers rather than, survival, absence of the disease, or some other measure of long-term success.<sup>29</sup> For example, in AIDS, testing for a period long enough to determine whether there is a high long-term survival rate would not be appropriate because of the large number of years it would take. Such a trial be impractical. In this case, a surrogate, such as a decline in viral particles in the blood, may be considered an acceptable marker. Similarly, markers are used for chronic diseases such as diabetes because of the length of time needed to prove that the drug actually inhibits the onset of complications.

There is a risk of using surrogate markers, however, because they may not adequately predict the therapeutic effectiveness (clinical benefit) of the drug candidate. In such a case, a trial could show significant positive results based on the surrogate chosen, and the drug would be approved. When used by the general patient population, however, it is possible that drug may not improve the patients' well-being to any significant degree. For this reason, for any drug that uses surrogate endpoints to gain market approval, the FDA will require a clinical trial after that approval to "resolve remaining uncertainty" about the ability of the surrogate endpoint to accurately predict clear clinical benefit.<sup>30</sup>

Phase II involves the first use of a control group — a test group of patients to whom a placebo or another drug is given — which allows the clearest means of proving whether the drug is successful and of determining its side effects. The use of placebos is becoming less common in favor of existing treatments where possible. Control groups also provide the means of eliminating confounding factors (factors that may have the same effect as the drug being tested but are unrelated to the drug's actions). A drug effect — desired or otherwise — must show up in a statistically significant manner among the participants of the test group in order to be considered definitive.<sup>31</sup> Use of a control group should be a double-blind procedure: neither the patients nor the physicians administering the treatment should know which group is getting the therapy being investigated. Typically, phase II trials include 50 to 500 participants, last about two years, and cost about \$20 million.<sup>32</sup>

Phase III trials determine the effectiveness of the drug and any important side effects. The testing in this phase is designed to match as closely as possible how the drug would be used if marketed. Often, several controlled studies (studies using control groups) take place at different locations (called multi-center studies), and each study must follow the same protocols. The group of patients included in the test are selected based on characteristics defined in the phase II trials. An important factor for this phase is to get patients with just the right level of illness to test efficacy — patients too ill may not live through the trial and those not ill enough may not show

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<sup>29</sup>Drews, *In Quest of Tomorrow's Medicine*, 132.

<sup>30</sup>21 CFR 314.510

<sup>31</sup>Zivan, "Understanding Clinical Trials," 73.

<sup>32</sup>*Ibid.*, 73.

significant improvement.<sup>33</sup> While such a group is not strictly representative of the entire population of patients with that disease, it is a necessary compromise in order to ensure a feasible trial.

The goal of the phase III trial is authoritative demonstration of a drug's effectiveness as defined by the end points determined in the phase II trials. A control group is used and a statistically significant number of test group patients must attain those end points for the study to be considered pivotal. Usually two or more pivotal trials are required to secure FDA approval unless the first trial is particularly positive. A large fraction (about 80%) of the data used for FDA approval applications arises from phase III trials.<sup>34</sup> If the results of the first phase III trial are ambiguous, a redesigned trial is usually held with a more restricted group of patients or with other changed factors. The data from the first trial usually determines the changes, if any, that need to be made in the follow-up trial.

The ideal Phase III trial is a double-blind, crossover trial. Crossover means that the test and control groups switch half-way through the trial. If the tested drug produces dramatic improvements, trials may be stopped before scheduled completion, with the approval of FDA, to make the drug available to everyone suffering from the disease. Phase III trials typically involve anywhere from 300 to 30,000 participants, run for three to five years, and cost about \$45 million.<sup>35</sup>

**General Features.** During the clinical trials, companies are required to follow certain standards and procedures to ensure good clinical practice.<sup>36</sup> As part of the IND filed with the FDA, the company must provide a complete description of the procedures it will follow in the clinical trials, including how it will meet the standards of good clinical practice. The FDA must approve those procedures before trials begin. The FDA issues guidelines about trial procedures, but they do not have the force of law. The FDA also has oversight responsibility over the trials and has the right to stop them at any time if it believes the participants may be at excessive risk.

The FDA also requires two other conditions to be met before trials can begin: informed consent by the participants and the establishment of an Institutional Review Board (IRB).<sup>37</sup> Patients participating in trials must sign a written, informed consent form explaining — to the extent possible — all of the potential risks about the study. The IRB, made up of patients' advocates, health-care professionals, and nonprofessionals, must oversee the trial, permit it to begin, and stop the trial if necessary. A Data Safety Monitoring Board is also established to monitor safety and other aspects. It, too, can recommend stopping the trial before it is completed.

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<sup>33</sup>Aldridge, *Magic Molecules*, 48.

<sup>34</sup>Drews, *In Quest of Tomorrow's Medicine*, 134.

<sup>35</sup>Zivan, "Understanding Clinical Trials," 75.

<sup>36</sup>*Ibid.*, 70-72.

<sup>37</sup>U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *From Test Tube to Patient: Improving Health through Human Drugs*, DHHS (FDA) 99-3168, September 1999, 25.

Costs of clinical trials, as noted above for each of the phases, are substantial and are usually borne by the drug companies. The costs include organizing and running the trials (done by physicians), data verification, analysis, and support personnel, as well as payments to physicians and nurses caring for participants. They do not include the cost of capital which, as noted below, is usually included when calculating total pharmaceutical R&D costs and is substantial. Because of the cost of these trials, pharmaceutical companies will almost always limit the drugs tested to those that have the potential for large markets.<sup>38</sup>

Upon completion of phase III trials, if the results prove positive, a New Drug Approval application (NDA) is filed with the Food and Drug Administration requesting approval to market the drug.<sup>39</sup> This application must contain a description of the drug chemistry, manufacturing processes, labeling (instructions for use of the drug), preclinical pharmacology and toxicology, pharmacokinetics (drug action in the body) and bioavailability in humans, and data and analysis from the clinical trials. Supporting information includes a description of clinical safety, patient information, and other relevant information. These applications are quite extensive, ranging up to several tens-of-thousands of pages in length.<sup>40</sup>

If approval is granted, the drug can be marketed. Assessment of the drug, however, does not stop at that point. Even though phase III trials consist of a large number of participants, it is impractical to make them so large that all conceivable adverse reactions can be determined. Therefore, postmarket surveillance must be carried out to determine if there are any safety concerns that did not show up during the clinical trials. This activity usually does not use controlled studies as is the case for phase II and phase III trials, but rather relies on observations of physicians prescribing the drug. Pharmaceutical companies are required to file adverse drug reaction (ADR) reports with the FDA on a regular basis. The marketing pharmaceutical company usually recruits physicians to monitor the actions of the drug on patients to whom it has been prescribed. On occasion, serious reactions show up that result in the drug being removed from the market, such as was the case with the diabetes drug Rezulin, which caused the deaths of several people taking the drug.<sup>41</sup>

It is also possible that FDA, as a condition of marketing approval, may require a firm to carry out a study to obtain more safety information after the drug is on the market. As noted above, such is the case for pre-approval trials that are based on surrogate endpoints. If such a study involves a clinical trial, it is labeled as a phase IV trial. It is also possible that new uses (indications) for the drug will be found during the phase IV trials.

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<sup>38</sup>Drews, *In Quest of Tomorrow's Medicine*, 135.

<sup>39</sup>For a description of the FDA, see Congressional Research Service, *Food and Drug Administration: Selected Funding and Policy Issues for FY2000*, by Donna Vogt, 95-422 SPR, February 27, 2000.

<sup>40</sup>Drews, *In Quest of Tomorrow's Medicine*, 137.

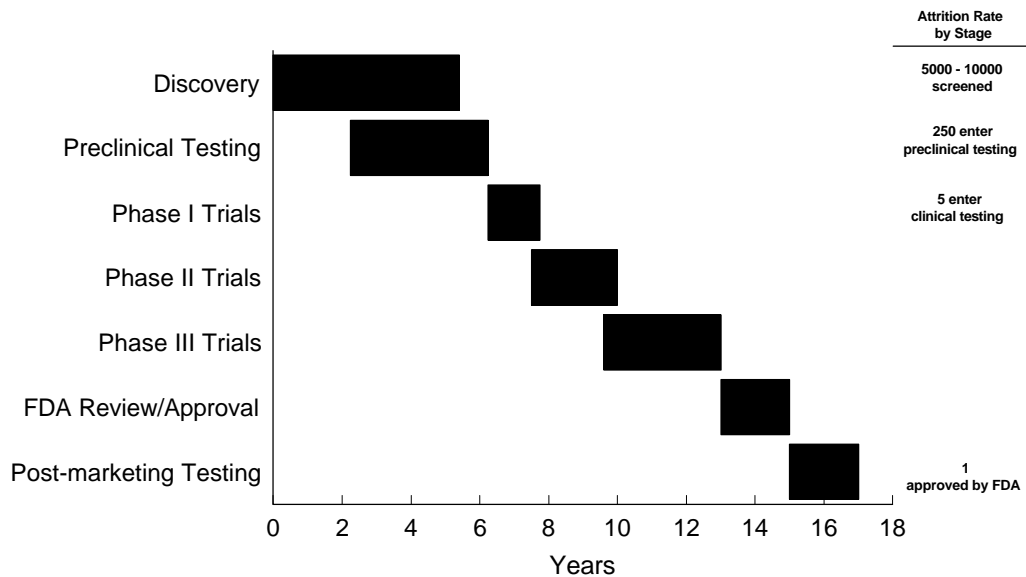
<sup>41</sup>David Willman, "The Rise and Fall of the Killer Drug Rezulin," *Los Angeles Times*, June 4, 2000, Section A1.

## Discussion

This section presents a discussion of three topics that are of particular importance in any consideration of the pharmaceutical R&D process: the time required to complete the process (drug development time), the cost of R&D to bring a drug to market, and the allocation of costs among the various components of the drug development cycle.

**Development Time.** As indicated above, the time it takes to go from the start of the drug discovery phase to the successful marketing of a drug is typically several

**Figure 1. Drug Development Time and Attrition Rate**



years. In addition, there is substantial attrition of drug candidates along the way. Figure 1, adapted from the Pharmaceutical Research and Manufacturers of America (PhRMA) 2000 Industry Profile, shows both of these characteristics.<sup>42</sup> The figure shows that the entire process takes on average about 15 years to marketing approval, with the clinical trials phase taking up about 7 years or 47% of the time. Furthermore, total drug development time has lengthened over the past 40 years.<sup>43</sup> In the 1960s, the average development time to approval from the onset of drug discovery (first synthesis of a drug candidate for initial laboratory screening) was about 8.1 years. In the 1970s, the average time was 11 years, in the 1980s it was 14.2 years, and in the early 1990s, it had grown to about 14.9 years. The attrition rate of drug candidates is also evident in the figure, which shows that for every drug approved by FDA, about

<sup>42</sup>PhRMA, *Industry Profile – 2000*, 32.

<sup>43</sup>PhRMA, *Industry Profile – 2000*, 34.



5,000 to 10,000 candidates were initially considered. Of course, nearly all of those candidates were eliminated by the time clinical trials commenced.

The length of the process has resulted in substantial effort over the years of trying to reduce the time taken for the various stages. For example, the chart shows that the average time for FDA approval is about two years. The average period for approval has dropped significantly in recent years, going from about 30 months in 1990 to about 12.6 months in 1999.<sup>44</sup> A sharp drop occurred from 1993 to 1994 and again from 1997 to 1998. The former was a result of the Prescription Drug User Fee Act of 1993, which provided FDA with funds to hire several hundred additional examiners. The latter coincides with the year the Food and Drug Administration Modernization Act of 1997 took effect. Nevertheless, the approval period remains relatively short — about 15% of the entire process — and the declines in recent years have not stopped the trend toward a longer drug development cycle.

The lengthy period for clinical trials has made them a major target for acceleration as well. There has been some progress on that front as the average length of trials has dropped from 7.2 years for those underway during the 1993 to 1995 period to 5.9 years for those underway during the 1996 to 1998 period.<sup>45</sup> Nevertheless, the need to obtain detailed information about potential side effects and the requirements for unambiguous results on an investigational drug's effectiveness mean that trials are likely to continue to require substantial periods of time — several years — for the foreseeable future.

The other major contributor to development time is the preclinical phase consisting of drug discovery and preclinical testing. How long drug discovery takes, of course, depends on how many compounds must be screened to come up with attractive drug candidates. If a candidate is discovered early in the process, the period can be considerably shortened. That is the basic reason for the wide range estimated for drug discovery — 2 to 10 years — given in the above chart. Drug discovery now is largely a rational systematic process compared to the trial and error approach that was dominant a few decades ago (see above), although the number of candidates that must be screened has not greatly changed. Indeed with the growing application of combinational chemistry, the number of candidates screened has probably grown. The “bottleneck” in drug discovery is not finding promising candidates — i.e., those that bind with the targets — but selecting those candidates that are also likely to become successful drugs.<sup>46</sup>

Drug researchers, however, hope that recent advances in biotechnology will result in a substantial decrease in time required for drug discovery. Biotechnology appears to be providing a way to accelerate and systematize the research process at

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<sup>44</sup>PhRMA, *Industry Profile – 2000*, 33.

<sup>45</sup>Zivan, “Understanding Clinical Trials,” 73.

<sup>46</sup>David Searls, “Using bioinformatics in gene and drug discovery”, *Drug Discovery Today*, 5 (April 2000), 136.

its beginning stages during the search for candidate drugs.<sup>47</sup> Important goals are the development of more precise drugs with fewer side effects (so-called smart drugs), development of susceptibility markers to treat diseases before onset, production on a large scale of replacement human proteins (e.g., insulin for diabetes treatment and erythropoietin for cancer treatment), and elimination of contamination resulting from the use of human or animal raw material sources for drug chemicals.

The science of genomics — the study of the human genome — facilitates the investigation of the underlying, genetic cause of diseases and how drugs work. This approach opens up the possibility of developing theoretical frameworks to identify therapies. Technologies emerging from genomics might be able to provide ways to systematically produce and test new molecules that are candidate drugs. One such process already in use is the comparison of DNA sequenced from diseased tissue with those in DNA databases.<sup>48</sup> If a match is found and the protein expression characteristics of the DNA in the database are known, it may be possible to determine the proteins encoded by the diseased sample. If so, drug target identification can be significantly facilitated with a consequent reduction in drug discovery time. Such comparisons are made possible by the field of bioinformatics, which applies advanced computer systems and technology to biology.

Eventually, it is likely to be possible to extend bioinformatics to play a major role in identification of drug candidates. Such computer-aided design processes have already been put to use and played a critical role in developing AIDS drugs. The HIV protease (the enzyme used by the virus to make proteins needed to infect cells) was modeled in this way and led to the protease inhibitor.<sup>49</sup> Full realization of this step toward computer-aided design of drugs is likely to be facilitated by identifying and determining the properties of all the proteins expressed by the human genome. This operation, called proteomics, involves both the identification of the protein and a determination of its physical structure.<sup>50</sup> Finally, gene therapy — the replacement of errors in the genetic code to prevent the expression faulty proteins or to ensure the expression of needed proteins — is being examined as a potential way to prevent the onset of a genetically caused disease in the first place. Because thousands of diseases are completely or primarily the result of genetic defects, such methods could prove to be very important for future drug development

Advances in molecular biology also give promise to reducing the cost and duration of clinical trials. There is hope that the emerging field of pharmacogenomics or pharmacogenetics — understanding the genetic basis for differing drug response — will result in the development of drugs that will be more effective and have fewer adverse side effects than current drugs. Basically, this process uses the genetic profile of an individual affected by a disease to predict the response of that person to a given medicine. Researchers hope that such predictions can remove much of the uncertainty that now exists about whether a drug will work. As a result, faster and more effective

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<sup>47</sup>PhRMA, *Industry Profile – 2000*, 9-13.

<sup>48</sup>Ken Howard, “The Bioinformatics Gold Rush,” *Scientific American*, 283 (July 2000), 59.

<sup>49</sup>Aldrige, *Magic Molecules*, 39.

<sup>50</sup>Carol Ezzell, “Beyond the Human Genome,” *Scientific American*, 283 (July 2000), 64.

clinical trials for new drug therapies should be possible, leading to more rapid drug approval.<sup>51</sup> Finally, drugs could be designed that are tailored to an individual.<sup>52</sup> In that last case, of course, the clinical trials would be meaningless. If drug development does reach this level of sophistication, different drug approval processes will be required.

While there is much promise in these advances, there are numerous and difficult challenges to surmount if they are to be widely applied to drug development. The mapping of the human genome, while a substantial achievement, is only one step. The targets of drugs, proteins, remain to be understood and surveyed in a way that will facilitate the search for new drug candidates.<sup>53</sup> The enterprise of proteomics will be long and costly and is just now getting underway.<sup>54</sup> Because protein structures are very complicated and are an essential feature in determining a protein's function, such surveys require a three-dimensional image of the protein (structural genomics). Obtaining these images requires the use of complex X-ray crystallography.

As noted above, only about 500 drug targets have currently been identified, a very small fraction of all of proteins in the body. While not all proteins will end up as drug targets, some estimates are that the human genome map will eventually yield up to 10,000 new targets.<sup>55</sup> Another challenge is that the proteins most important for drug design, e.g., membrane proteins that control input to a cell, appear to be those most difficult to survey because of difficulties in determining their structure.<sup>56</sup>

Identification of drug targets, of course, is only part of the battle. Drug candidates must be discovered that bind to the target. Identifying such candidates require experimental procedures that are still very complex and subject to many failures. Furthermore, while a particular molecule might bind with a given drug target and result in apparent therapeutic action, that is no guarantee that it will be successful as a drug. Doses at toxic levels may be required to achieve the desired results. In other cases, the investigatory drug molecule may bind to other proteins, resulting in unwanted side effects.

In addition, it is too soon to tell just how effective the genetic advances will be in shortening the time required for clinical trials. The response of an individual to a drug is very complex and it is likely to take some time before researchers, regulators, and consumers will accept more specific, shorter trials to prove drug safety and efficacy. Nevertheless, recent advances are substantial and hold out much hope for a dramatically improved pharmaceutical R&D process.

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<sup>51</sup>Allen D. Roses, "Pharmacogenetics and future drug development and delivery," *Lancet*, 355 (April 15, 2000), 1358.

<sup>52</sup>Eric S. Grace, *Biotechnology Unzipped: Promises and Realities*, 88.

<sup>53</sup>Robert Service, "Structural Genomics Offers High-Speed Look at Proteins," *Science*, 287 (March 17, 2000), 1954-56.

<sup>54</sup>*Ibid.*, 1956.

<sup>55</sup>Aldridge, *Magic Molecules*, 257.

<sup>56</sup>Service, "Structural Genomics," 1956.

**R&D Costs.** The cost of developing a typical drug (pharmaceutical R&D) is not well established. One source cites costs for R&D for a successful drug of about \$116 million in 1976, about \$287 million in 1987, about \$359 million in 1990, and about \$500 million in 1996.<sup>57</sup> All are in 1990 dollars. The 1990 figure was obtained from a study carried out by the Office of Technology Assessment and is the cost estimated before taxes.<sup>58</sup> The most recent figure is an estimate provided by PhRMA and is based on drugs introduced in 1990.<sup>59</sup> These estimates are before taxes, and cover both successful and unsuccessful drug development attempts.

Also important is how R&D costs are allocated among the various components of the R&D process. The chart shown in Figure 2, based on data from PhRMA, provides a graphical display of how those costs are allocated.<sup>60</sup> It is clear from the

**Figure 2. R&D Cost Allocations by Stage - 1998**

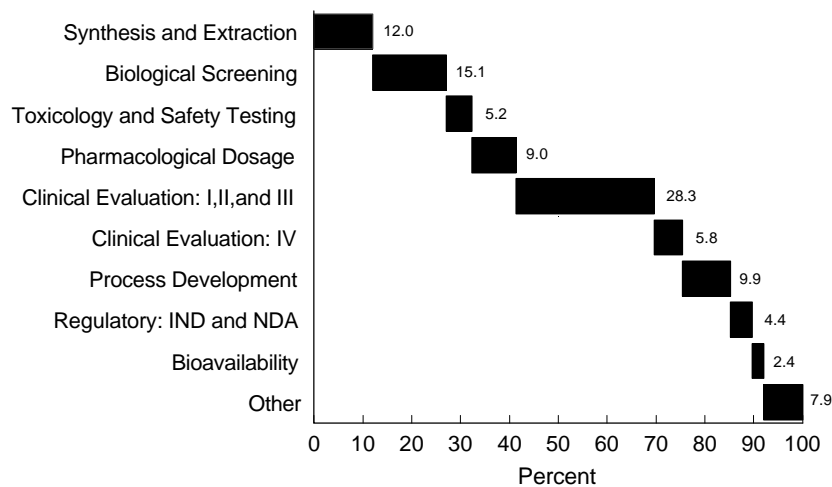


chart that clinical trials consume the major share of the costs, about 28.3% for Phases I through III, and an additional 5.8% for Phase IV. In addition, the actual drug discovery phase — synthesis and extraction and biological screening — requires about 27.1%.

**General Cost Issues** A major importance of the cost of pharmaceutical R&D lies in the claim made by the industry that prescription drug prices in the United States are justified by the high cost of developing new drugs. As a consequence, any debate about those prices usually includes a debate about the costs of doing pharmaceutical

<sup>57</sup>Drews, *In Quest of Tomorrow's Medicine*, 149

<sup>58</sup>U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards*, OTA-H-522, February 1993, 16.

<sup>59</sup>PhRMA, *Industry Profile – 2000*, 25.

<sup>60</sup> *Ibid.*, 26.

R&D. While it is beyond the scope of this report to present a detailed analysis of those costs, a few points can be made about them that may be important for any debate over costs.

First, there have not been many detailed studies of the costs done by disinterested groups. The last such study was the OTA effort which was completed in 1993. Data used for that study were obtained on drugs developed during the 1980s.<sup>61</sup> No results have been reported on drugs developed in the last 10 years that might have benefitted significantly from the recent advances in molecular biology.

Second, the calculation of those pharmaceutical R&D costs that have been reported all contain a factor accounting for the cost of capital.<sup>62</sup> This cost element accounts for the opportunity cost of money invested in the R&D process. In other words, the funds used for R&D could have been used for other investments (opportunities) that will yield a return. Those 'lost' opportunities are accounted for by including the forgone returns as part of the cost of performing R&D. Including such costs is a standard accounting practice used by all of industry in computing R&D costs. In the OTA estimate, opportunity costs constitute about 65% of the total R&D cost for a typical drug. The key element in calculating the foregone returns is the cost of capital, which is determined by the discount rate assumed. A change of a few percentage points in that rate can make a substantial difference in the total R&D cost.<sup>63</sup> While most analysts agree with the inclusion of opportunity costs, there is dispute over the size of the discount rate assumed. Industry officials generally agreed with the rates used by OTA but some critics argued they were too high.<sup>64</sup>

Third, there is a disagreement about whether pretax or after-tax costs are the more appropriate figure for pharmaceutical R&D costs.<sup>65</sup> For the OTA study, the after-tax estimate is \$194 million compared to the pretax estimate of \$359 million. This difference is substantial. It should be noted, however, that the marginal tax rate used in the OTA study, 46%, has since been reduced to 34%. As a result, the pretax/after-tax differences calculated on current pharmaceutical R&D costs would be considerably smaller than in the OTA case, but still large. On the other hand, the

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<sup>61</sup>OTA, *Pharmaceutical R&D*, 48-54.

<sup>62</sup>It should be remembered that costs presented in this section include the cost of capital while those in the section on clinical trials above do not.

<sup>63</sup>Joseph A. DiMasi, "Trends in Drug Development Costs, Times, and Risks," *Drug Information Journal*, 29 (May 1995), 375.

<sup>64</sup>George Anders, "Vital Statistic: Disputed Cost of Creating a Drug," *The Wall Street Journal*, November 9, 1993, B1.

<sup>65</sup>Ibid., B5.

OTA calculation did not account for the research and experimentation tax credit<sup>66</sup> or any tax credits available for orphan drug development.<sup>67</sup>

A fourth consideration is whether the sales of successful drugs cover pharmaceutical R&D costs. According to the industry, a 1994 study found that only three out of ten pharmaceuticals introduced from 1980 to 1984 had enough sales to cover average R&D costs per drug.<sup>68</sup> Those sales, however, were sufficient to cover the industry's total R&D costs. In fact, the OTA study found that the internal rate of return (IRR) for the entire pharmaceutical industry from 1976 to 1987 exceeded the returns to other firms by about two to three percentage points.<sup>69</sup> This IRR differs from the standard accounting return on assets that are usually reported in publically available statements from individual firms.<sup>70</sup> Comparison of the return on assets for the same companies for which the OTA IRR comparison was made showed that pharmaceutical companies outperformed other firms by four to six percentage points over the 1976 to 1988 period. While there has been no more recent study of IRR comparison, data on return on assets from 1995 through 1999 continues to show that pharmaceuticals as a group outpaces all other industry groups and in nearly all cases the margin is greater than two percentage points.<sup>71</sup> It should be noted that the pharmaceutical industry generally contends that return on assets overstates the industry's profitability because drug patents are not counted as assets in standard accounting practices used to determine this measure.

**Contribution of Federal R&D Funding.** Another point of discussion is the contribution of federally-funded biomedical research to pharmaceutical development.<sup>72</sup> Nearly all of that research is supported by the National Institutes of Health (NIH).<sup>73</sup> In FY2001, NIH's total budget was \$20.31 billion, about 60% of which goes for basic biomedical research and most of the remainder for clinical research. NIH basic research focuses on the biological, chemical, and molecular understanding of disease. Drug development is not its mission, although drugs do

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<sup>66</sup>Congressional Research Service, *The Research and Experimentation Tax Credit: Current Law and Selected Policy Issues for 106th Congress*, by Gary Guenther, RL30479, Jan. 23, 2001.

<sup>67</sup>Orphan drugs are those for which the potential market is small — 200,000 or fewer patients. A 50% tax credit on qualifying R&D is provided for those drugs as well as seven years of market exclusivity (P.L. No. 97-414, 96 Stat. 2049 (1983) (codified at 21 U.S.C. § 360aa et seq.)).

<sup>68</sup>PhRMA, *Industry Profile – 2000*, 25.

<sup>69</sup>OTA, *Pharmaceutical R&D*, 24.

<sup>70</sup>For an discussion of the difference between IRR and the return on assets see OTA, *Pharmaceutical R&D*, 95-96.

<sup>71</sup>See, for example, “Most profitable industries,” *Fortune*, April 17, 2000, F-27.

<sup>72</sup>For an extended discussion of federal support of pharmaceutical R&D, see OTA, *Pharmaceutical R&D*, 201-235.

<sup>73</sup>The National Science Foundation, the Department of Energy, the Department of Defense, the Veterans Administration, and the National Aeronautics and Space Administration, and the Environmental Protection Agency also fund biomedical research.

result from discoveries made by NIH-funded research.<sup>74</sup> While in some instances testing of actual drug candidates may be funded by NIH,<sup>75</sup> in most cases it is the knowledge of the disease mechanisms gained from the NIH-funded research that allows pharmaceutical companies to proceed with drug discovery.<sup>76</sup> It is common for the pharmaceutical industry to develop drugs from scientific discoveries made by researchers supported by the NIH.<sup>77</sup> In addition, over the last 20 years, Congress has enacted a number of laws to enable cooperative research arrangements between industry and government in order to facilitate the commercial application of knowledge discovered through federally-funded research.<sup>78</sup> These laws have been particularly successful in the areas of biomedical research.<sup>79</sup>

It seems clear that the pharmaceutical R&D cost estimates reported above understate the true cost by not including federally funded R&D that contributed to the ultimate development of the drug. That is, if the pharmaceutical industry had to pay for all of the basic research now funded by NIH, it is likely that the average cost of R&D to bring a drug to market would increase, perhaps substantially.<sup>80</sup> While the industry does fund a significant amount of basic research, most of its R&D funding is directed at drug discovery and development, and clinical trials. Estimates of the contribution of NIH-funded research to pharmaceutical R&D costs are usually not attempted because of the great difficulty of assigning basic research costs to specific innovations. There is generally not a direct linear relationship between basic research and specific innovations, but rather the connections are quite complex.

For the NIH-funded research that is focused on specific drug development, the allocation of costs is less difficult but still uncertain. The OTA study estimated that about 14% of preclinical pharmaceutical R&D in 1988 was funded by NIH. NIH also funds clinical research, as noted above, although most of that support is usually reserved for high-risk therapies not likely to yield high profits, and that would be of limited benefit to the industry.<sup>81</sup> A certain fraction of NIH clinical trial funds does directly support pharmaceuticals, however, and OTA estimated that about 11% of all pharmaceutical R&D funds allocated to clinical trials in 1988 came from NIH.

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<sup>74</sup>Iain M. Cockburn and Rebecca Henderson, "Publicly Funded Science and the Productivity of the Pharmaceutical Industry," *NBER Conference on Science and Public Policy*, National Bureau of Economic Research, Washington, DC, April 2000, 12.

<sup>75</sup>OTA, *Pharmaceutical R&D*, 202.

<sup>76</sup>Cockburn, "Publicly Funded Science," 12.

<sup>77</sup>Jeff Gerth and Sheryl Gay Stolberg, "Drug Companies Profit From Research Supported by Taxpayers," *New York Times*, April 23, 2000.

<sup>78</sup>Congressional Research Service, *Federal R&D, Drug Discovery, and Pricing: Insights from the NIH-University-Industry Relationship*, by Wendy Schacht, RL30585, June 19, 2000.

<sup>79</sup>Jeff Gerth, *New York Times*, April 23, 2000.

<sup>80</sup>If total R&D expenditures did not change, the increased cost of R&D for a typical drug under these circumstances would likely mean that fewer new drugs would be developed.

<sup>81</sup>Zivan, "Understanding Clinical Trials," 75.

These figures suggest that the cost of pharmaceutical R&D to the industry for a typical drug would increase significantly if it had to absorb all of the costs that now directly support drug development but which are funded by NIH. It would likely be an even greater increase if the costs of all of the contributing basic research now funded by NIH could somehow be allocated to drug development. The outcome of such a situation could be a noticeable increase in the price of an average drug to the extent those prices cover R&D costs. Furthermore, to the extent the total industry expenditures on R&D did not grow, the number of new drugs developed would likely decrease. Therefore, one could argue that federal funding of biomedical research is helping to keep drug prices down. This possibility is indirectly raised by analysis that puts the rate of return to the industry of public biomedical research funding at 30%.<sup>82</sup>

This benefit appears substantial, but that is no guarantee that another allocation of public and private R&D resources — e.g., the pharmaceutical industry supporting all biomedical research — could not produce a higher return. While it is not the purpose of this report to present an analysis of this issue, it is worthwhile to present some considerations important to that analysis. If industry had to fund the basic research that contributes to drug development that is now funded by NIH, it probably would not support all of the research now funded by NIH. Industry would very likely restrict funding to that it believed most relevant to pharmaceutical development, and total national spending on biomedical R&D — public and private sectors — would be less than is now the case. In this hypothetical situation where industry would absorb all basic biomedical research costs needed for drug development, the cost of R&D to develop a typical drug would increase from current estimates. Because total spending on basic biomedical research would be lower than is currently the case, however, the return on that investment, in terms of pharmaceuticals produced, would be higher than current estimates, provided no change in output — discovery and marketing of new pharmaceuticals — occurred.

Whether productivity could remain the same under this scenario would depend primarily on the pharmaceutical industry being able to select just the basic research now funded by NIH needed to maintain industry productivity. As discussed above, such research includes both basic research that is directly related to drug development and basic research that advances general biomedical knowledge important for drug discovery. It is very unlikely that the industry would be able to make such a selection given the uncertain nature of basic research. In addition, it is possible, in this hypothetical situation, that important knowledge that would be essential to the advances of biomedicine in the more distant future — 10 to 20 years — would not be forthcoming because the research had not been done. Another concern about this scenario is what happens to the basic research results. It is unlikely that a firm would be willing to make these results widely available if it believed they were important for its economic future. As a result, researchers outside that firm would not have access to new biomedical knowledge that may be critical to other advances in medicine, with a consequent loss to the public.

Also, even though the economic benefit from NIH research quoted above appears substantial, that is no guarantee that the public is adequately compensated for

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<sup>82</sup>Cockburn, “Publicly Funded Science,” 18.



the subsidy that federally funded biomedical R&D provides to the industry. There are other factors that must be accounted for to assess that issue thoroughly.<sup>83</sup>

***Implications of Biomedical Advances.*** The high and apparently growing cost of pharmaceutical R&D puts a premium on any advances that will slow that growth or even reduce costs. Shorter drug development time would mean smaller direct outlays for R&D. Furthermore, because the opportunity costs (described above) accumulate on an annual basis, a shorter development time would mean that this contribution to pharmaceutical R&D costs would decline as well. The biomedical advances discussed above in the section on drug development time, if successful, offer that opportunity. Cost mitigation would be especially true if those advances allowed a significant decrease in the time required for the clinical trials, which are the biggest single component of the cost of drug development.

Reduced pharmaceutical R&D costs for a typical drug could, in turn, have at least two advantages. First, it is possible that lower pharmaceutical prices will result. Second, drug companies may be more willing to undertake research on drugs that have a more limited market — that is, on drugs that attack diseases that afflict only a relatively small number of people. Now, such research is generally limited because the companies cannot expect to recover their R&D costs with sales of those drugs.<sup>84</sup> If shorter development times significantly reduce such costs, the prospect of being able to recover costs from a more limited-market drug should increase. Coupled with the increase in precision in targeting diseases that is promised by these new techniques, research on such drugs could expand. Another benefit of shorter development time would likely be greater total revenues to the firm patenting the drug because less of the patent period would be taken up by drug development. It is possible that such an occurrence could also lower drug prices because the firm would have more time to make a return on its drug development investment.

There are factors, however, that may limit the extent to which application of these biomedical advances can result in lower drug development costs. First, as noted above, there is uncertainty about how well these advances will translate into more effective drug development with shorter development times. Second, application of these techniques is likely to require very large initial investments in equipment and facilities. The genetic profile process, for example, requires complex and extensive robotic systems that are not typically found in conventional drug discovery processes. Nevertheless, to the extent these new drug development techniques are successful, the promise of lower drug R&D costs and more specific drugs appears real.

## **Congressional Concerns**

There are several issues associated with drug development (pharmaceutical R&D) that may be of interest to Congress. Three of the more important issues concern the cost of pharmaceutical R&D and its relation to prescription drug prices,

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<sup>83</sup>CRS, *Federal R&D, Drug Discovery and Pricing*, 18-19.

<sup>84</sup>The Orphan Drug Act (see footnote 67) provides incentives to pharmaceutical manufacturers to develop drugs for diseases that afflict 200,000 people or fewer and may not otherwise generate sufficient returns to justify the necessary R&D.

the role of federally funded R&D (primarily NIH) in pharmaceutical development, and federal oversight of the drug development process.

**Drug Development Costs.** The options open to Congress to affect the cost of pharmaceutical R&D appear to be limited. It has taken steps, as noted above, to shorten the time of drug approval. Further shortening may not be acceptable to Congress or the public, however, and is not likely to affect costs very much while the rest of the development cycle remains as long as is now the case. Congress has also granted a general research and experimentation tax credit as well as a specific R&D tax credit for the development of orphan drugs. As argued above, however, significant changes in those costs will probably require major advances in drug discovery that also permit much shorter clinical trial periods. These advances will be almost solely dependent on progress in science and technology. If a dramatic shortening of clinical trials appears scientifically feasible, however, drug approval regulations may have to be modified in order to accommodate those new conditions.

**Federal Biomedical R&D Funding.** One area where congressional action may significantly affect pharmaceutical R&D costs in the longer-run is through federal biomedical R&D funding. Congress has provided NIH with substantial year-to-year increases in its budget. From FY1998 to FY2001, the budget has grown from \$13.6 billion to \$20.3 billion, a 49% increase. For FY2002, the Administration is requesting \$23.1 billion, a 13.8% increase over the current fiscal year. It is on track to double by 2003 to a level of about \$27 billion, although it is not certain that doubling will happen by that time. The primary reason for this increase is to accelerate the push towards the development of effective therapies for the major diseases afflicting humankind. As noted above, there appears to be little overlap between the R&D funded by NIH and that funded by the pharmaceutical industry. Furthermore, the research sponsored and performed by NIH appears to be quite important to the industry.

As NIH funding grows, however, there is the possibility that a greater portion of it will be used in areas that are also being funded by the pharmaceutical industry, including biotechnology firms. This is true of the human genome project and is likely to be true of much of the followup work. In particular, both NIH and the industry are funding work in structural genomics,<sup>85</sup> which is an essential part of proteomics, the next step beyond mapping the human genome. NIH is funding pilot centers to develop methods of determining the structure of proteins, while industry has several projects underway. Because knowledge of protein structures is critical to drug discovery, it seems clear that it is important for industry to fund it. That does not imply that NIH should not fund any research in structural genomics — knowledge of protein structures is also important for the understanding of fundamental biological processes — but caution is needed to avoid unproductive duplication. It should be noted that the synergy between federal and private funding of the human genome project has probably accelerated completion of that effort.

A related issue concerns ownership of the information generated by both public and private funding. The debate over whether human genome data generated by

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<sup>85</sup>Service, “Structural Genomics”, 1954.

private companies should be made available to the public when the government is also funding such work is likely to be repeated with protein structure data. The fact that data generated by both efforts were complementary helped to smooth possible conflicts in the case of the genome. Because protein structure data is likely to be even more important to the pharmaceutical industry than genome data, however, data ownership issues may become more serious. If conflicts do emerge, NIH may end up duplicating much of the industry work to ensure broad public access. Congressional oversight of situations where both the industry and NIH independently pursue research related to drug development may be heightened.

**Clinical Trial Practice.** While Congress has direct oversight of clinical trials supported by NIH, congressional authority over trials supported by the pharmaceutical companies is more tenuous and indirect. It is primarily through its oversight of the FDA, which, as noted, has oversight and some regulatory responsibility over privately run clinical trials. Aside from the possibility of major changes in clinical trial practice resulting from scientific advances, there are some aspects of current practices that Congress may wish to examine. Two such topics are: patient protection and conflict of interest. While neither is likely to affect the length of time that clinical trials now take, they could have a significant effect on the quality and safety of such trials.

The death in September 1999, of a patient undergoing an experimental gene therapy treatment at the University of Pennsylvania has highlighted the possible dangers of participation in clinical research.<sup>86</sup> While trials are overseen by an Institutional Review Board and individuals must sign informed consent statements prior to participation in a trial, there are concerns that adequate protection for patient safety is not always present. Such protection is essential if trials are to continue to secure the numbers of patients needed to adequately test drug candidates. Currently, the Department of Health and Human Services, with the establishment of the Office of Human Research Protection, is significantly expanding its efforts in this area.<sup>87</sup>

Recently, concern about conflict of interest on the part of physician-researchers involved in clinical trials has grown.<sup>88</sup> The potential for conflict is a result of a growing number of academic researchers being involved in research funded by the pharmaceutical and biotechnology industries. Since the beginning of the modern pharmaceutical industry, there has been a close relationship between the industry and universities.<sup>89</sup> The last two decades have seen a growth of cooperative research

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<sup>86</sup>Zivan, "Understanding Clinical Trials," 72.

<sup>87</sup>Bruce Agnew, "Koski takes over HHS Office for Human Research Protection, plans a tough approach on conflict of interest and overall human-subjects protections," *Washington Fax*, F-D-C Reports, Inc., September 7, 2000.

<sup>88</sup>See e.g., David Korn, "Conflicts of Interest in Biomedical Research," *JAMA*, 284 (Nov. 1, 2000), 2234-6.

<sup>89</sup>Ralph Landau, Basil Achilladelis, and Alexander Scriabine, *Pharmaceutical Innovation: Revolutionizing Human Health* (Philadelphia: Chemical Heritage Press, 1999), 38.

between industry and NIH-funded academic researchers.<sup>90</sup> As a consequence, the linkage between academic scientists and the pharmaceutical industry has intensified substantially. Some have argued that this growing tie poses a risk to public confidence in the results of clinical trials performed by these researchers.<sup>91</sup>

Because industry contracts with universities for a significant fraction of the clinical trials it undertakes — about 40% of industry funding for clinical trials in 1998 went to universities<sup>92</sup> — it seems important that effective safeguards be in place to protect against abuses resulting from potential conflicts of interest. Currently, regulations from the Public Health Service (PHS), issued in 1995, deal with conflict of interest in federally funded clinical research. In addition, the FDA has regulations, issued in 1998, requiring financial disclosure from clinical investigators. They leave management of potential conflicts of interest up to the individual institutions, and there is considerable variation among those institutions.<sup>93</sup> Some argue that certain kinds of financial ties between academic researchers and the pharmaceutical industry should be prohibited altogether.<sup>94</sup> Others argue that such ties do not need to be banned, but a better job of managing financial conflicts of interest is needed by the institutions themselves.<sup>95</sup>

In 2000, the Department of Health and Human Services began consideration of new conflict-of-interest rules. The director of the then newly established Office for Human Research Protection (OHRP) announced that the office would seek to establish more stringent conflict of interest standards.<sup>96</sup> On January 10, 2001, the OHRP issued a “draft interim guidance document” on financial relationships in clinical research. The document also contained a request for comments due by March 2, 2001. The new guidelines are not meant to replace existing regulations of PHS agencies, including FDA, but to “help IRBs [Institutional Review Boards], Clinical Investigators, and Institutions in carrying out their responsibilities to protect human subjects” under existing regulations.<sup>97</sup> The draft guidelines recommend, among other things, that universities limit the direct participation in clinical research of scientists

<sup>90</sup>CRS, *Federal R&D, Drug Discovery and Pricing*, 4-7.

<sup>91</sup>Catherine D. DeAngelis, “Conflict of Interest and the Public Trust,” *JAMA*, 284 (Nov. 1, 2000), 2238.

<sup>92</sup>Thomas Bodenheimer, “Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry,” *The New England Journal of Medicine*, 342 (May 18, 2000), 1540.

<sup>93</sup>Mildred K. Cho, Ryo Shohara, and Anna Schissel, “Policies on Faculty Conflicts of Interest at US Universities,” *JAMA*, 284 (Nov. 1, 2000), 2204.

<sup>94</sup>Marcia Angell, “Is Academic Medicine for Sale?” *The New England Journal of Medicine*, 342 (May 18, 2000), 1518.

<sup>95</sup>Jordan J. Cohen, “Trust Us to Make a Difference,” *AAMC Annual Meeting*, October 29, 2000, Chicago, IL. [<http://www.aamc.org/newsroom/speeches/00amspee.htm>]

<sup>96</sup>Bruce Agnew, *Washington Fax*, September 7, 2000.

<sup>97</sup>Public Health Service, U.S. Department of Health and Human Services, *Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interest and Human Subject Protection*, January 10, 2001, [<http://ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm>].

who could be influenced by financial ties to the sponsoring firm; that research institutions consider whether it is appropriate for its scientists to participate in research sponsored by firms in which the institution has investments; and that conflict-of-interest committees should be established by universities to review financial links of individual scientists.

In addition, the Association of American Medical Colleges (AAMC) established a task force to look at the issue. On February 13, 2001, a group of leaders of the nation's medical schools receiving the most federal research funds issued a set of recommendations for the AAMC task force to consider.<sup>98</sup> These recommendations include, among other things, that financial interests of researchers taking part in trials be disclosed to the IRBs and that they be reviewed periodically. The recommendations were endorsed by the AAMC. The group also recommended that responsibility for such disclosure be expanded to everyone directly involved in the clinical research.

While these recommendations appear to move towards better control of potential conflict-of-interest problems, they still would leave much of the management of those situations with the institutions. In addition, the contract research organizations (CROs) are only addressed to the extent academic researchers are involved in the trials managed by the CROs. It appears, therefore, that monitoring of both university and CRO efforts will be important to ensure that public confidence in clinical trials and in the academic biomedical research community does not suffer.

## Conclusions

The debate about whether to include prescription drug benefits in Medicare has raised the visibility of pharmaceutical R&D. As noted in this report, pharmaceutical R&D is a complex, costly, and time-consuming process. It is also noted, however, that advances in molecular biology in recent years hold the promise of dramatically changing the way pharmaceutical R&D is carried out. These changes could shorten substantially the time it takes to bring a drug to market from initial research and therefore significantly affect the cost of drug development. How fast such changes may come about, however, could depend heavily on further research in molecular biology and the mechanisms of disease. Congress has strongly supported biomedical research in recent years and there are calls for continuing to make it a high priority. In addition to biomedical research funding levels and priorities, issues related to human subject protection and conflict of interest are likely to affect the evolution of pharmaceutical R&D and, therefore, its costs.

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<sup>98</sup>Shirley Haley, "Leaders from top-funded medical schools release recommendations for managing financial conflicts of interest: principles will be basis of AAMC task force deliberations," *Washington Fax*, F-D-C Reports, Inc., February 14, 2001.

## Appendix A

### A Brief History of Pharmaceutical Research and Development

Although substances have been used to treat disease for centuries, systematic pharmaceutical research did not begin until the late 19<sup>th</sup> century when chemistry had reached the point where its principles could be applied to medical problems and pharmacology became a scientific discipline. A major linkage occurred in the chemical dye industry when it was discovered that certain dyes have a chemical affinity for biological materials. German scientist, Paul Ehrlich (1854-1915), a pioneer in pharmaceutical research, determined that this “chemoreceptor” property would be different for certain organisms, such as parasites and cancer cells, than the host tissue, and this difference allowed the development of chemicals that could be used for therapeutic purposes.<sup>99</sup> He based this observation on experiments in which he synthesized a large number of compounds and testing each for its ability to destroy the organism without being toxic to the host. The basis for this process was Ehrlich’s observation that certain chemicals would selectively attach themselves to proteins.<sup>100</sup>

At the same time, developments in chemistry permitted the isolation of active chemicals from plants that showed medicinal benefits. This was followed by efforts to standardize drug preparations. Medicinal chemistry also developed when it was discovered that coaltar could be used to create synthetic drugs. In addition, the science of pharmacology — the measurement and testing of the effectiveness of drugs — was being developed. These developments all combined to provide the impetus for the creation, from 1880 to about 1930, of the modern pharmaceutical industry.

The discovery of penicillin in 1929 led to the discovery of other antibiotics using the science of microbiology. The concepts of enzymes and receptors arising from the study of biochemistry began to play a role in drug discovery when they were found to be good targets for drug research. An important discovery was that receptors serve as switches to generate or receive signals to the cell, and that these receptors could be either blocked or turned on by chemicals.<sup>101</sup> During World War II, the demand for penicillin and other antibiotics allowed the drug companies to develop the infrastructure and organization to undertake major R&D efforts. After the war, drug research accelerated because of the numerous opportunities and the large profits new drugs generated.<sup>102</sup>

Drug discovery, however, was still largely a trial and error process. That is, compounds were tried that were obtained somewhat haphazardly from libraries of molecules available to drug researchers. Those libraries were built up over the years

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<sup>99</sup>Drews, “Drug Discovery: A Historical Perspective,” 1960.

<sup>100</sup>Landau, et.al., *Pharmaceutical Innovation: Revolutionizing Human Health*, 39-40

<sup>101</sup>Drews, “Drug Discovery,” 1961.

<sup>102</sup>National Research Council, “U.S. Industry in 2000: Studies in Competitive Performance”, *Pharmaceuticals and Biotechnology*, (National Academy Press, Washington, DC, 1999), 368.

because it was thought that the compounds, many of which were obtained from natural substances, might have some therapeutic value. In the 1960s and 1970s, advances in both life science research and chemistry greatly improved the drug research process, making it less random.<sup>103</sup> The focus of the life science research was the physiology of the cell, which allowed for design of specific drugs and greater understanding of how drugs worked than had been discovered through trial and error. In particular, as knowledge grew, drugs could be designed to inhibit well-defined proteins. Also, once the actions of certain drugs were understood, that knowledge was often used for greater understanding of the underlying disease, and, in turn, the design of new drugs. Advances in chemistry permitted systematic generation and testing of chemical compounds (combinational chemistry) as candidate drugs. The advances in both fields combined to make the drug discovery process more rational.

The 1960s also saw the development of the modern process for getting a drug to market. Beginning in 1938, drugs were required by the federal government to prove that they were safe.<sup>104</sup> It was not until the thalidomide episodes in the late 1950s, however, that the requirement for clinical evidence was established to gain approval to market a new drug. The Kefauver-Harris amendments passed by Congress in 1962 required a proof-of-efficacy and gave the FDA regulatory control over the necessary clinical trials.<sup>105</sup> At that time, the present-day process of elaborate clinical trials was established for determining the efficacy of candidate drugs.

Advances in molecular biology and biotechnology in the 1970s and 1980s have also contributed to drug research.<sup>106</sup> Biotechnology was first applied to drug development by bringing about dramatic increases in the production of certain drugs such as insulin whose efficacy was already established. Biotechnology was also used to enhance the search for new drugs. As molecular biology progressed, these two paths merged so that medical biotechnology is now primarily focused on the search for new drugs such as protease inhibitors used to treat AIDS, which must be produced by genetic engineering techniques.

Drug research over the last 120 years has evolved from a trial and error method, where many compounds were tried for their potential therapeutic value with only a little understanding of how they might work, to a much more rational approach that is based on a large body of knowledge about the origin of disease and workings of pharmaceuticals. Currently, drug discovery makes use of many disciplines, including chemistry, pharmacology, microbiology, and biochemistry. Sources for candidate drugs still include natural substances (such drugs are called biologics) as well as synthetic molecules created by chemical or biotechnology processes.

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<sup>103</sup>Landau, et.al., *Pharmaceutical Innovation*, 91-92.

<sup>104</sup>This action resulted from a tragic situation when 107 people died while taking sulfanilamide in a liquid form. Drews, *In Quest of Tomorrow's Medicine*, 141.

<sup>105</sup>National Research Council, U.S. Industry in 2000, 375.

<sup>106</sup>*Ibid.*, 378.