

November 2006

NEW DRUG DEVELOPMENT

Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts



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Highlights

Highlights of [GAO-07-49](#), a report to congressional requesters

Why GAO Did This Study

Drug development is complex and costly, requiring the testing of numerous chemical compounds for their potential to treat disease. Before a new drug can be marketed in the United States, a new drug application (NDA), which includes scientific and clinical data, must be approved by the Food and Drug Administration (FDA). Recent scientific advances have raised expectations that an increasing number of new and innovative drugs would soon be developed to more effectively prevent, treat, and cure serious illnesses. However, industry analysts and the FDA have reported that new drug development, and in particular, development of new molecular entities (NMEs)—potentially innovative drugs containing ingredients that have never been marketed in the United States—has become stagnant.

GAO was asked to provide information on (1) trends in the pharmaceutical industry's reported research and development expenses as well as trends in the number of NDAs submitted to, and approved by, FDA; and (2) experts' views on factors accounting for these trends and their suggestions for expediting and enhancing drug development. GAO analyzed data from FDA on all 1,264 NDAs submitted to the agency from 1993 through 2004. GAO also convened a panel of experts and interviewed other drug development experts and analysts to identify factors affecting, and suggestions for enhancing, drug development.

www.gao.gov/cgi-bin/getrpt?GAO-07-49. To view the full product, including the scope and methodology, click on the link above. For more information, contact Leslie G. Aronovitz at aronovitzl@gao.gov or (312) 220-7600.

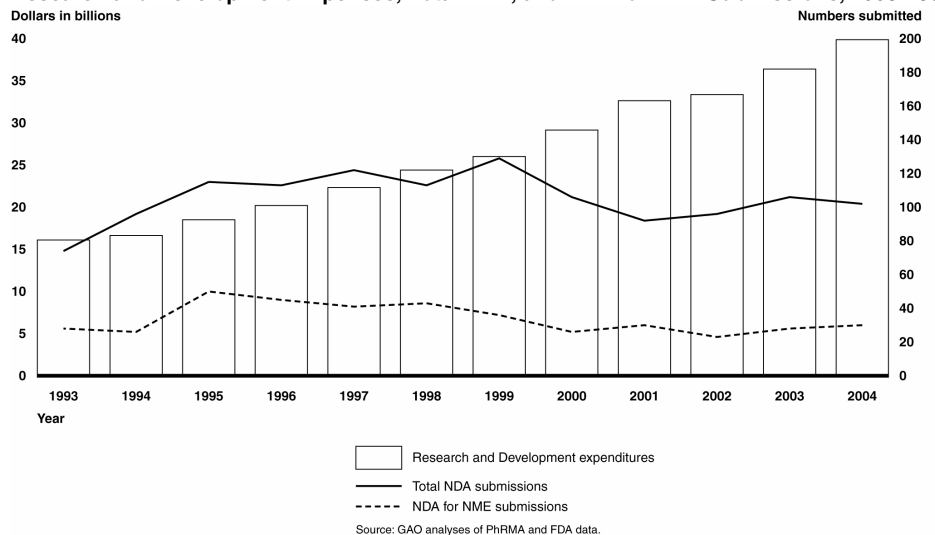
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What GAO Found

Although the pharmaceutical industry reported substantial increases in annual research and development costs, the number of NDAs submitted to, and approved by, FDA has not been commensurate with these investments. From 1993 through 2004, industry reported annual inflation-adjusted research and development expenses steadily increased from nearly \$16 billion to nearly \$40 billion—a 147 percent increase. In contrast, the number of NDAs submitted annually to FDA increased at a slower rate—38 percent over this period. Similarly, the number of NDAs submitted to FDA for NMEs increased by only 7 percent over this period. FDA approved most NDA applications—76 percent overall, but the numbers of NDAs and NDAs for NMEs it approved annually have generally been declining since 1996.

Research and Development Expenses, Total NDA, and NDA for NME Submissions, 1993-2004



According to experts, several factors have hampered drug development. These include limitations on the scientific understanding of how to translate research discoveries into safe and effective drugs, business decisions by the pharmaceutical industry, uncertainty regarding regulatory standards for determining whether a drug should be approved, and certain intellectual property protections. These factors have been cited as affecting the number of drugs developed, the cost and length of the drug development process, as well as the types of drugs being produced. To address these issues, experts offered suggestions including increasing the number of scientists who can translate drug discoveries into effective new medicines and allowing conditional approval of certain drugs based on shorter clinical trials using fewer numbers of patients. In its comments on a draft of this report, the Department of Health and Human Services provided clarifications, which GAO incorporated as appropriate.

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Abbreviations

AAMC	Association of American Medical Colleges
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IND	investigational new drug application
NAS	National Academy of Sciences
NDA	new drug application
NME	new molecular entity
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America

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United States Government Accountability Office
Washington, DC 20548

November 17, 2006

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor and Pensions
United States Senate

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives

The Honorable Richard J. Durbin
United States Senate

Before a new drug can be marketed in the United States, it must be approved by the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS). To gain approval, drug sponsors¹ must submit a new drug application (NDA) to FDA containing scientific and clinical data. FDA reviews the NDA to determine whether the new drug is safe and effective for its intended use. The submission of an NDA typically follows a long period of research and development. To develop a new drug, researchers and scientists identify and test numerous chemical compounds for their potential to treat disease. On average, drug sponsors can spend over 13 years studying the benefits and risks of a new compound, and several hundred millions of dollars completing these studies before seeking FDA's approval. About 1 out of every 10,000 chemical compounds initially tested for their potential as new medicines is found safe and effective, and eventually approved by FDA, making the drug discovery and development process complex, time consuming, and costly. Although high costs and failure rates make drug discovery and development risky, creating a safe and effective new drug can be rewarding for both the sponsor and the public. A highly successful new drug can generate significant annual sales, and can provide cures or

¹A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable provisions of laws, such as the Federal Food, Drug, and Cosmetic Act and related regulations. The sponsor is usually an individual, partnership, corporation, government agency, manufacturer, or scientific institution.

help treat the symptoms of diseases and illnesses affecting millions of people.

Significant scientific advances have raised new hope for the prevention, treatment, and cure of serious illnesses. For example, the decoding, or sequencing of the human genome, advances in medical imaging, and new technologies that enable drug researchers to rapidly synthesize numerous compounds, created expectations that the pharmaceutical industry would soon be producing an increasing number of new and innovative drugs to more effectively treat disease. However, over the past several years it has become widely recognized throughout the industry that the productivity of its research and development expenditures has been declining; that is, the number of new drugs being produced has generally declined while research and development expenses have been steadily increasing. Similarly, FDA and analysts reported that pharmaceutical research and development investments were not producing the expected results and that innovation in the pharmaceutical industry had become stagnant.² In addition, FDA reported that the industry was predominantly submitting NDAs for variations of existing drugs, rather than for new and innovative drugs, such as new molecular entities (NMEs)—potentially innovative drugs containing active chemical substances that have never been approved for marketing in the United States in any form. In response to the declining productivity of drug development, FDA launched two separate initiatives—one in 2003 and another in 2004—to help facilitate drug development.³ In its 2004 initiative, it specifically cited an urgent need to improve the drug development process and to enhance collaboration among the government, industry, and academia.

You raised questions regarding the numbers of new drugs being produced, and in particular, those drugs representing important therapeutic advances in effectively treating disease—such as NMEs. This report provides (1) data regarding trends in the pharmaceutical industry’s reported research and development expenses as well as trends in the number of NDAs and NDAs for NMEs submitted to, and approved by, FDA; and (2) experts’ views on factors accounting for these trends, and their

²For example, see FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004).

³See FDA, *Improving Innovation in Medical Technology: Beyond 2002* (Jan. 31, 2003) and FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004).

suggestions for expediting the drug development process and increasing the productivity of research and development efforts.

To determine trends in the pharmaceutical industry's reported research and development expenditures, we obtained information from the Pharmaceutical Research and Manufacturers of America (PhRMA)⁴ for the period 1993 through 2004, and adjusted it for inflation to 2004 dollars.⁵ We did not independently verify these amounts; however, many researchers have cited these data as the best available information. To identify trends in the number of submissions and approvals of NDAs, we obtained and analyzed data from FDA on all 1,264 NDAs submitted to the agency for review from January 1, 1993, through December 31, 2004. The information we reviewed on these 1,264 NDAs included their status—whether the applications had been approved, withdrawn, or were still under FDA's review. In addition, we obtained FDA's initial assessment of the NDAs' review priority, whether the NDAs were for NMEs, specific dates documenting when an NDA was submitted, and all of FDA's decisions regarding the applications. We also discussed the results of our data analyses with FDA officials to obtain their perspective on drug development trends.

To determine factors underlying new drug development trends, we interviewed experts from the pharmaceutical industry, academia, and a public interest group who possess knowledge of issues that have had an impact on drug development. We also interviewed some pharmaceutical industry analysts who had previously published reports on drug development issues. In addition, we organized a panel of experts—with assistance from the National Academy of Sciences (NAS)—that included experts from academia, the pharmaceutical industry, and patient advocates. We held this panel in order to provide a forum where widely recognized experts could collectively discuss drug development issues. The panel was not designed to build consensus on any of the issues discussed. The panelists provided their individual views, which do not necessarily reflect those of the organizations with which they were

⁴PhRMA represents pharmaceutical research and biotechnology companies.

⁵We obtained PhRMA's data for this period to correspond with data we obtained from FDA. In 1992, FDA implemented a new system for classifying NDAs, and in 1993, specified time-frame goals for reviewing NDAs were established. We therefore obtained data beginning with 1993 to generally correspond to these changes, and requested data through 2004, which was the most recent year with a complete set of NDA submission data at the time of our request.

affiliated or the NAS. We asked these experts to identify factors affecting the development of new drugs, and in particular, innovative drugs such as NMEs. As part of the panel discussion, we asked them to identify incentives or actions that could expedite drug development and enhance the development of drugs that offer therapeutic advances in effectively treating diseases. Further, we reviewed and analyzed previously published reports and articles issued by pharmaceutical industry analysts, academic researchers, and the federal government. We reviewed these reports and articles to identify factors influencing drug development, and suggestions for expediting this process. Detailed information on our methodology is in appendix I and a list of the panelists is in appendix II. We conducted our work from July 2005 through October 2006 in accordance with generally accepted government auditing standards.

Results in Brief

Although the pharmaceutical industry has reported substantial increases in annual research and development costs, the number of NDAs submitted to, and approved by, FDA has not been commensurate with these investments. From 1993 to 2004, the industry reported that annual research and development expenses steadily increased from nearly \$16 billion to nearly \$40 billion in real terms—a 147 percent increase.⁶ In contrast, the number of NDAs submitted annually increased at a lower rate—38 percent over this period—and generally declined over the past several years. The number of NDAs submitted annually increased from 74 to 129, or by 74 percent, between 1993 and 1999, and generally declined after 1999. In 2004, sponsors submitted 102 applications to FDA—a 21 percent decrease from the 1999 level. Similarly, the number of NDAs submitted to FDA for NMEs increased by only 7 percent over this period, and generally declined since 1995. From 1993 through 1995, the number of NDAs submitted for NMEs increased, but declined by 40 percent between 1995 and 2004. The percentage of NDAs submitted that were for NMEs also generally declined after 1995. These submission trends indicate that the productivity of research and development investments has declined. Regarding approval trends, FDA eventually approved most NDAs—961 or 76 percent overall—and the percentage approved each year has remained relatively constant. However, the overall number of NDAs—and NMEs in particular—approved annually has generally been declining since 1996, which corresponds with the decline in submissions.

⁶Real growth reflects growth after the effects of inflation are removed.

Results from the discussion among panel members, our interviews with drug development experts and analysts, and our review of academic and industry reports identified several factors affecting the types of drugs being developed, and the length, costs, and failure rates of drug development. These factors include limitations on the scientific understanding of how to translate chemical and biological discoveries into safe and effective drugs; business decisions by the pharmaceutical industry that influence the types of drugs developed; uncertainty regarding regulatory standards for determining whether a drug should be approved as safe and effective; and certain intellectual property protections that can discourage innovation. Together, these factors have been cited as affecting the cost and length of the drug development process, as well as the types of drugs being produced. Faced with these issues, some of the panelists, other experts we contacted, and the literature we reviewed, suggested ways to expedite drug development and find more innovative drugs. These include generating greater numbers of scientists who possess the skills needed to translate drug discoveries into effective new medicines; restructuring regulation of the drug review process to allow for conditional approval of drugs for therapeutic areas that currently lack effective treatments based on shorter clinical trials using fewer numbers of patients; and altering the length of patent terms to encourage innovation. Some of the experts have cautioned that adequate measures to ensure safety need to be implemented along with any changes to expedite the regulatory review process.

In its comments on a draft of this report, HHS provided clarifications, which we incorporated as appropriate.

Background

FDA is responsible for helping to ensure the safety and effectiveness of drugs marketed in the United States. It oversees the drug development process, reviews drug sponsors' applications for the approval of new drugs, and monitors the safety and efficacy of drugs once they are available for sale. As part of its responsibilities, FDA assists drug sponsors in designing clinical trials to test drugs on humans, reviews proposals for conducting such trials, and approves drugs for sale in the United States based on its determination that a drug's clinical benefits outweigh its potential health risks, and is safe and effective. Prior to a manufacturer's marketing of a drug, FDA reviews drug labels and accompanying materials to ensure they are consistent with applicable laws and regulations. Among other things, labels must include information on the drug's usage, for example, the medical conditions and patient populations for which it has been tested and approved as safe and effective.

The Drug Discovery, Development, and Review Process

The process of bringing a new drug to the market consists of four main stages—drug discovery, preclinical testing, clinical trials which involve testing on volunteers, and FDA review. During these stages, scientists from the government, academia, and the private sector conduct extensive research and testing to identify safe and effective medicines. The entire drug discovery, development, and review process takes, on average, 15 years to complete.

During the first stage—commonly referred to as drug discovery—numerous researchers from pharmaceutical companies, academia, and government search for and identify promising chemical entities, or compounds, capable of curing or treating diseases. During the second stage—preclinical testing—these compounds are tested in laboratories and in animals to predict whether a drug is likely to be safe and effective on humans. Most compounds fail during these first two stages; according to PhRMA, only 5 in every 10,000 compounds, on average, successfully completes these two stages. In general, these two stages typically take a total of 6½ years to successfully complete for a particular compound.

If the compound is found to be promising, a drug sponsor may decide to test it as a new drug on humans, and proceeds to the third stage—clinical trials. Before doing so, a sponsor must submit an investigational new drug application (IND)⁷ that summarizes the data that have been collected on the compound and outlines plans for the clinical trials.⁸ Generally, clinical trials may begin 30 days after FDA receives the IND, unless FDA orders a delay. FDA does not issue a formal approval to the sponsor regarding an IND submission, but it can prohibit the start of a clinical trial if, for example, it determines that human volunteers would be exposed to an unreasonable and significant risk of illness or injury. As described below, the clinical trial stage consists of three phases, known as Phase 1, 2, and 3 clinical trials.

⁷Drugs studied under INDs are compounds that are under development and essentially provide the pipeline of drugs that ultimately become the subjects of NDAs that are submitted to FDA for approval.

⁸There are two classes of INDs—commercial and noncommercial. Commercial INDs are submitted primarily by companies whose ultimate goal is to submit an NDA to obtain marketing approval for a new product. Noncommercial INDs are filed for noncommercial research purposes. For example, a physician might submit a research IND to study potential medicinal uses for an unapproved drug. In this report, all references to INDs refer to commercial INDs.

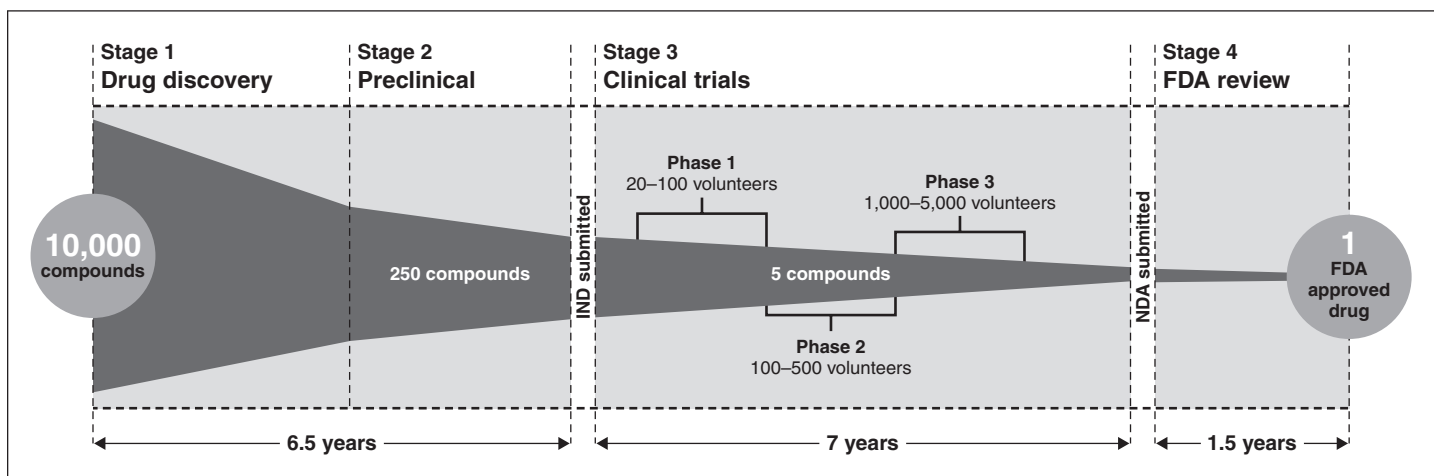
In Phase 1 clinical trials, sponsors typically conduct safety studies on about 20 to 100 healthy volunteers. Potential side effects are identified and various dosage levels are determined. In Phase 2 clinical trials, the drug is typically tested on approximately 100 to 500 volunteers who have a particular disease to determine the drug's effectiveness. In Phase 3 clinical trials, the drug is typically tested on about 1,000 to 5,000 volunteers, to determine the drug's safety and effectiveness. According to PhRMA, on average, one out of every five drugs successfully completes all three clinical testing phases—that is, is found safe and effective by the drug sponsor and submitted as an NDA to FDA for review and approval. On average, the three phases of the clinical trial stage take a total of 7 years to successfully complete.

The fourth and final stage is the FDA review stage, which covers FDA's review and final approval of NDAs. The review process begins when a sponsor submits an NDA to FDA. The NDA contains scientific and clinical data submitted by the sponsor intended to demonstrate that the drug is safe and effective for its proposed use. FDA evaluates data contained in the NDA to determine whether the drug meets these standards and if it should be approved.⁹ For those NDAs that are approved, it typically takes about 1½ years to complete the review process and obtain FDA's approval.

Figure 1 shows the amount of time, on average, for a successful new drug to move through and complete the four stages. It also illustrates that for every 10,000 compounds initially identified, only one, on average, will be found safe and effective, and be approved by FDA.

⁹For more information on the FDA review and approval process, see for example, GAO, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, [GAO-02-958](#) (Washington D.C.: September 17, 2002).

Figure 1: The Drug Discovery, Development, and Review Process



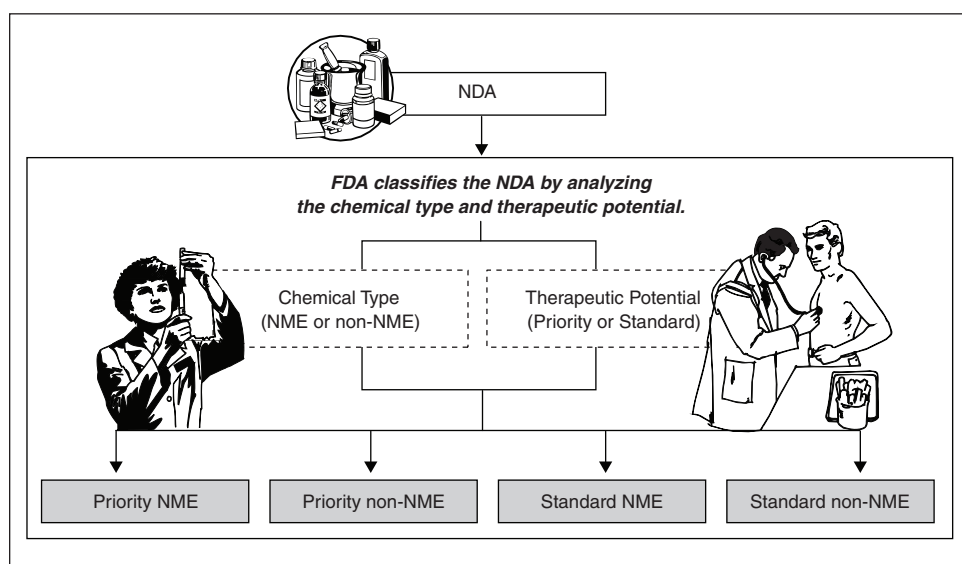
Source: Pharmaceutical Research and Manufacturers of America.

Upon receipt of an NDA, FDA will classify it in two ways—by its chemical type and its therapeutic potential. First, an NDA is classified into chemical types, one of which is an NME.¹⁰ Because NMEs contain active chemical substances never before approved for marketing in the United States, industry analysts and FDA generally consider them innovative. The other six classifications consist of non-NMEs, which are typically considered less innovative because they represent modifications to drugs already on the market. In most cases, the sponsor submitting an NDA for a non-NME has altered the original medicine to produce a drug with different features, such as a new dosage form or route of administration. Second, FDA classifies an NDA by its therapeutic potential. In doing so, FDA compares the NDA to existing products already on the market. Those that appear to have relatively significant therapeutic benefits in the treatment, diagnosis,

¹⁰FDA classifies NDAs into seven chemical types. These classifications are (1) NME, (2) new salt of previously approved drug (not a new molecular entity), (3) new formulation of previously approved drug (not a new salt or a new molecular entity), (4) new combination of two or more drugs, (5) already marketed drug product - duplication (i.e., new manufacturer), (6) new indication (claim) for already marketed drug (includes switch in marketing status from prescription to over the counter), and (7) already marketed drug product—no previously approved NDA—for example, according to an FDA official, a drug marketed prior to the creation of FDA, such as aspirin.

or prevention of a disease are classified as priority.¹¹ Those with little or no additional therapeutic benefits compared to existing products are classified by FDA as standard. As figure 2 shows, an NDA can be classified in one of four ways—priority NME, priority non-NME, standard NME, or standard non-NME.

Figure 2: FDA Classification of NDAs by Chemical Type and Therapeutic Potential



Source: GAO.

In response to concerns that FDA was taking too long to review and approve NDAs, the Prescription Drug User Fee Act (PDUFA)¹² was enacted in 1992. It provided FDA with additional resources in the form of user fees from the pharmaceutical and biotechnology industries to speed up the process of reviewing applications for new drugs and biological products, and established performance goals for FDA, including

¹¹FDA's Manual of Policies and Procedures notes that the priority designation is intended to direct overall attention and resources to the evaluation of applications that have the potential for providing significant therapeutic advances as compared to "standard" applications. It also states that the priority determination is based on conditions and information available at the time the application is filed. It is not intended to predict a drug's ultimate value or its eventual place in the market.

¹²Pub. L. No. 102-571, 106 Stat. 4491.

completing its review of a certain percentage of applications within certain time frames.¹³ PDUFA authorized FDA to collect these fees to supplement its annual appropriation for salaries and expenses, and use the additional funds to review applications more quickly.¹⁴ PDUFA was amended and reauthorized in 1997 and 2002 for an additional 5 years and established new performance goals for various aspects of the drug review process. For example, current goals state that FDA should complete its initial review and act on 90 percent of all priority NDAs within 6 months and 90 percent of all standard NDAs within 10 months. FDA uses these and other review time goals to assess its review timeliness, and issues an annual report on its performance to the President and Congress.¹⁵

The review process may span several review cycles. The first cycle begins when the NDA is submitted to and filed by FDA, indicating that the application is sufficiently complete to permit a substantive review. The first cycle ends when FDA has completed its review and responds by issuing an action letter to the sponsor. This could mean that FDA approved the application; told the sponsor it was approvable, but that more information was needed; or told the sponsor that the NDA contained significant weaknesses and was not approvable. If the application is approved in the first cycle, the total approval time is the length of that cycle. For those NDAs not approved during the first review—both approvable and not approvable—the second cycle begins when the sponsor files an amendment and resubmits the application and it is filed by FDA. The resubmission often contains additional studies, analyses, data, or clarifying information to address concerns raised by FDA in the previous review. As with the first cycle, this cycle ends when FDA has completed its review and issues an action letter to the sponsor. If the

¹³Biological products, or biologics, are derived from living sources—such as humans, animals, and microorganisms—as opposed to being chemically synthesized, and include vaccines and blood products.

¹⁴Under PDUFA, companies pay three types of user fees to FDA—application fees, establishment fees, and product fees. In most cases, a company seeking to market a new drug in the United States must pay an application fee to support the agency’s review process. Generally, companies also pay an annual establishment fee for each facility in which their products subject to PDUFA are manufactured and an annual product fee for marketed drugs for which no generic versions are available. For more information on PDUFA user fees see GAO, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, [GAO-02-958](#) (Washington D.C.: September 17, 2002).

¹⁵See: FDA, *FY 2004 Performance Report to the President and the Congress for the Prescription Drug User Fee Act*.

review process takes two or more cycles, the total approval time includes the time spent during the review cycles, plus the additional time the sponsor uses to address the issues raised by FDA.

FDA Response to Concerns Over the Number of Drugs Developed

Over the past several years, numerous industry analysts and FDA noted a decline in the submission of applications for NDAs overall, and for innovative drugs, such as NMEs.¹⁶ In light of this, in January 2003, FDA launched a broad initiative to improve the development and availability of innovative medical products, including new drugs.¹⁷ As part of this initiative, FDA sought to reduce: (1) the number of drugs requiring more than one review cycle, (2) overall approval times, and (3) development costs. To help accomplish this, FDA sought to improve the development and review process by educating drug sponsors on the type and extent of scientific data that must be present in the NDA's initial submission. Noting the decline in the number of NDAs, in 2004 FDA proposed a second, more targeted, initiative—known as the critical path initiative—to form a collaborative effort between government, industry, and academia.¹⁸ In doing so, FDA cited an urgent need for a new product development “tool kit” to enable researchers to more effectively translate basic research discoveries into safe and effective products. Such tools include better techniques of identifying safety problems as early as possible and better methods for demonstrating medical effectiveness; tools, which according to FDA, could help reduce the failure rates of drug development and increase the number of NDA submissions.

¹⁶For example see: American Enterprise Institute-Brookings Joint Center, *Shortening Drug Approval Times via Industry Funding of the FDA: Did Legislation Help or Hurt?* (Feb. 16, 2005).

¹⁷FDA, *Improving Innovation in Medical Technology: Beyond 2002* (Jan. 31, 2003).

¹⁸FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004).

Drug Development Trends Are Not Commensurate with Research and Development Expenditures

Overall, our analyses of drug development data revealed that increases in research and development expenditures from 1993 through 2004 have not led to a commensurate increase in NDAs submitted to FDA, including those classified as NMEs. Although the pharmaceutical industry reported a 147 percent real increase in annual research and development expenditures from 1993 through 2004, and an increasing number of INDs are being submitted to FDA, the number of new drugs developed has not grown in a similar manner. Compared to industry-reported research and development expenditures, the number of NDAs and NDAs for NMEs submitted to FDA over the period increased at a lower rate—by 38 percent and 7 percent respectively—which indicates that the productivity of the research and development investments has been declining. Furthermore, the majority of NDAs submitted to FDA were for non-NMEs, and thus represented modifications to existing drugs rather than newer and potentially more innovative drugs. FDA has consistently approved most of the NDAs submitted, with approval rates nearing 80 percent overall, and has been approving applications much more quickly in recent years. However, the actual numbers of drugs approved annually has been declining, reflecting the trends in NDA submissions.

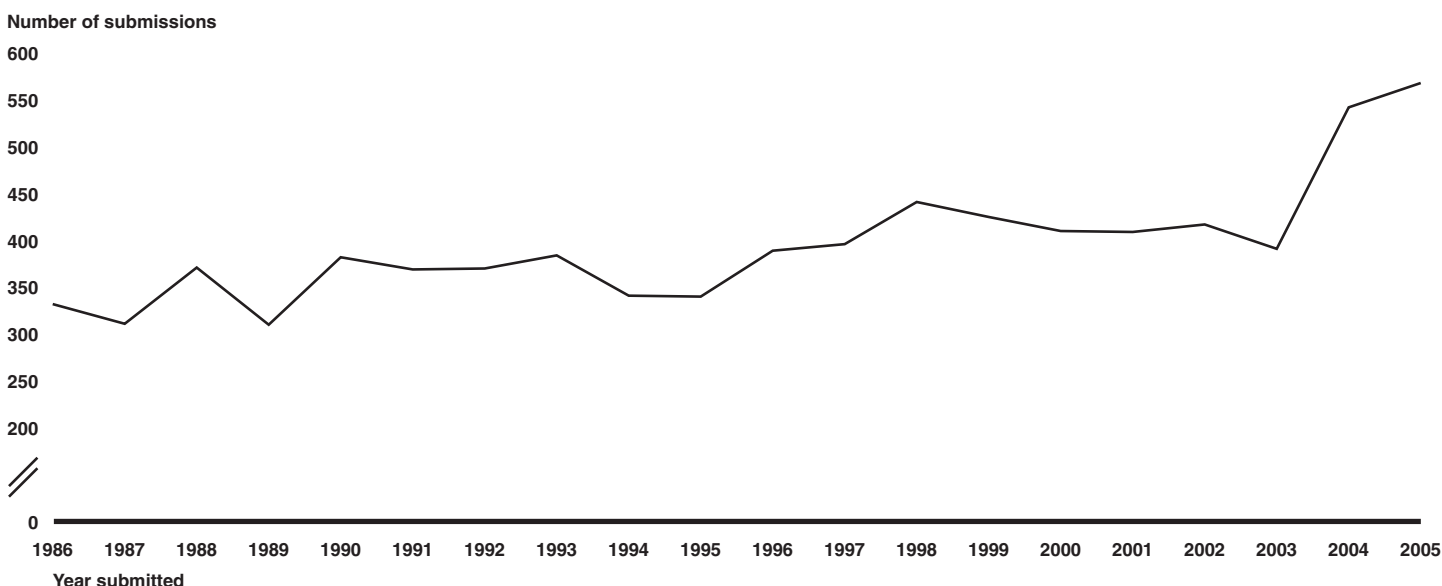
The Productivity Associated with Research and Development Expenditures Has Recently Declined

According to PhRMA and industry analysts, research and development expenditures are key to the development of new and innovative medical products, including pharmaceuticals. During the drug discovery and preclinical stages, research and development expenditures fund efforts to identify new compounds that could ultimately become INDs. Research and development expenditures during the clinical trial phases fund the studies needed to prove a drug is safe and effective, leading to a potential NDA submission. Our review of annual research and development expense data reported by PhRMA and IND submission data reported by FDA indicate that there have been substantial and consistent increases in these expenses over the past decade, and that the number of INDs submitted to FDA has been increasing. However, we found that these investments have not led to a commensurate increase in the number of NDAs and NMEs, and thus, the productivity of these investments has declined.

Figure 3, which shows the number of INDs that sponsors submitted to FDA from 1986 through 2005, indicates that there have been fluctuations in

the number of INDs submitted each year.¹⁹ However, in general, sponsors have been submitting an increasing number of INDs since 1986. Figure 3 also shows a 45 percent increase in IND submissions over the last 2 years.

Figure 3: IND Submissions, 1986-2005



Source: GAO analysis of FDA data.

Note: The data in this figure are for commercial INDs.

Despite the trends of increasing IND submissions and steady increases in research and development expenses, we found that the number of NDAs submitted to FDA has generally been declining over the past several years. Figure 4 shows the annual research and development expenses reported by PhRMA for 1993 through 2004 (adjusted for inflation to 2004 dollars), and the total number of NDAs (including those for NMEs) and NDAs for

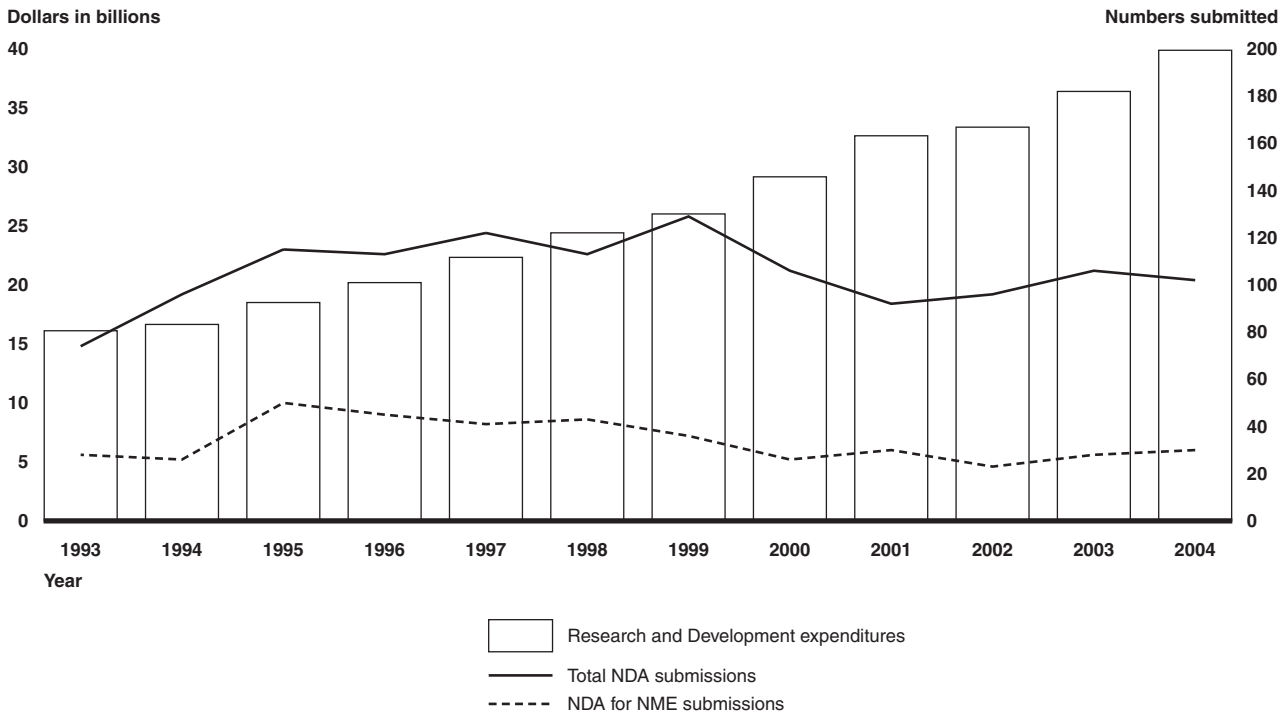
¹⁹We chose this time period for two reasons. First, because we obtained NDA data beginning with 1993 and it takes 7 years, on average, to successfully complete clinical trials, trends emerging from INDs submitted in 1986 could be reflected in NDA submission trends beginning in 1993. Second, 2005 was the most recent year for which we could obtain complete data from FDA.

NMEs submitted to FDA during the same period.²⁰ As figure 4 shows, annual research and development expenses grew consistently over the period. In 1993, the inflation-adjusted expenses were nearly \$15.7 billion, and grew to an estimated \$38.8 billion in 2004—a 147 percent real increase over the period.²¹ Our analysis also revealed that inflation-adjusted annual growth rates of the research and development expenses ranged from a low of just over 2 percent from 2001 to 2002, to over 11 percent from 1999 to 2000.

²⁰Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2005* (Washington, D.C.: Pharmaceutical Research and Manufacturers of America, 2005). Each year, PhRMA surveys its membership and requests information on the amount its members spent on research and development. According to PhRMA, these expenses include both domestic expenses and expenses incurred abroad. Domestic expenses include those incurred within the United States by PhRMA member companies. Expenses abroad include expenses incurred outside of the United States by U.S.-owned PhRMA member companies and expenses incurred outside the United States by the U.S. divisions of foreign-owned PhRMA member companies. Expenses incurred outside the United States by the foreign divisions of foreign-owned PhRMA member companies are not included. We did not independently verify these amounts. However, these data have been repeatedly cited, and they represent the best available information. For example, see Kaiser Family Foundation, *Prescription Drug Trends* (October 2004).

²¹According to our analysis of PhRMA's data, total research and development expenditures were 17 percent of total sales in 1993, and were 16 percent in 2004.

Figure 4: Research and Development Expenses (Constant 2004 Dollars), Total NDA, and NDA for NME Submission Trends, 1993-2004



Source: GAO analyses of PhRMA and FDA data.

In contrast to the steady and large increase in research and development expenditures, we found that the number of NDAs submitted annually increased at a lower rate—38 percent over this period—and has generally declined over the past several years. As figure 4 shows, there was initial growth followed by a general decline in submissions of all NDAs, including NDAs for NMEs, to FDA. For NDAs, figure 4 shows that the number submitted to FDA, in general, grew from 1993 through 1999. In 1993, sponsors submitted 74 NDAs to FDA. In 1999 this number grew to 129—a 74 percent increase from 1993. After 1999, however, NDA submissions generally declined, and in 2004, sponsors submitted 102 NDAs, which represented a 21 percent decrease from 1999 levels. Figure 4 also shows that the number of NDAs submitted to FDA for NMEs increased slightly over this 12-year period—by 7 percent. In addition, Figure 4 shows that the number of NMEs submitted to FDA peaked in 1995, and, for the most part, then began to decline. Although sponsors submitted 50 NMEs in 1995, this number fell to 30 in 2004, which represented a 40 percent decline. It

should be noted that submissions of NDAs for NMEs increased during the last 2 years of this time frame—rising from 23 in 2002, to 28 in 2003, and 30 in 2004.

Because it may take several years from the time research and development investments are made until the time a sponsor submits an NDA to FDA for approval, expenses in any given year are generally not related to NDA submissions in that year. Additionally, given the uncertain nature of research and development efforts, it is unlikely that expenditures and NDA submissions would grow at the same rate. However, given a 147 percent increase in research and development expenditures over the 12-year period, many analysts and experts assumed that the trend in NDA submissions would also generally be one of consistent increases. The NDA submission trends, combined with IND submission trends, indicate that the industry faces challenges in successfully completing the clinical testing stage, leading up to the submission of an NDA.

Most NDAs Were for Modifications to Existing Drugs

In addition to determining the overall trends in the number of NDAs and NMEs submitted to FDA, we used FDA chemical type and therapeutic potential classifications—NME, non-NME, priority, and standard—to make a general assessment of the level of innovation of the NDAs submitted. Any one NDA—regardless of whether it is for an NME or was granted priority status by FDA—may eventually turn out to be an innovative and uniquely therapeutic product. However, FDA and industry analysts use the chemical type and therapeutic potential classifications to make a general assessment of the innovative potential of NDAs at the time of submission. We used the four classifications as outlined in table 1 to rank the innovative potential of NDAs.²²

²²Based on our interviews with FDA officials and our review of prior studies, we determined there was a general consensus that the most important factor in assessing the innovative potential of an NDA was whether or not it was an NME.

Table 1: Ranking of Innovative Potential of NDAs Using Chemical Type and Therapeutic Potential Classifications

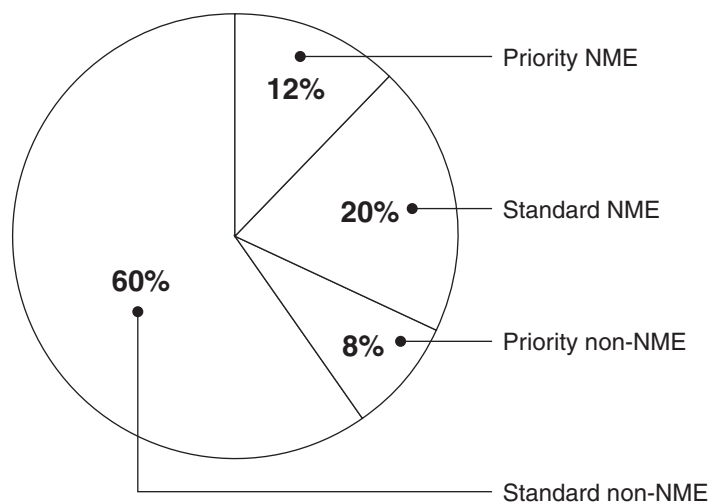
NDA submission type	Level of potential innovation
Priority NME	1
Standard NME	2
Priority non-NME	3
Standard non-NME	4

Source: GAO analysis of FDA chemical type and therapeutic potential classifications.

Note: The ranking of 1 represents the highest innovative potential, and 4, the lowest.

Based on how FDA classified the 1,264 NDAs submitted from 1993 through 2004, we determined the proportion of NDAs submitted by each of the four classifications. As figure 5 shows, 68 percent of the NDAs were classified as non-NMEs—those representing modifications to existing drugs, while the remaining 32 percent of the NDAs submitted were NMEs. The figure also shows that 12 percent of NDA submissions were for drugs in the priority NME classification—those representing the highest potential level of innovation.

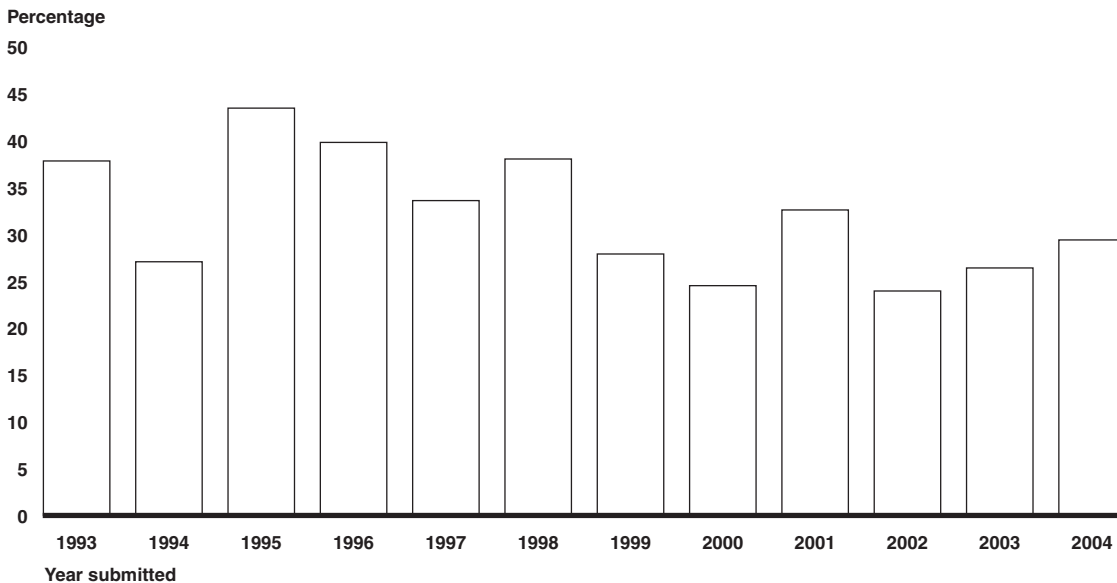
Figure 5: Proportion of 1,264 NDAs Submitted by Innovation Potential, 1993-2004



Source: GAO analysis of FDA data.

Based on FDA's classification of the 1,264 NDAs, we determined the percentage submitted each year that were NMEs and priority NMEs. Regarding NMEs, figure 6 shows that during the period 1993 through 2004, there was variation from year to year in the percentage of NDAs submitted that were NMEs. Figure 6 shows that this percentage ranged from a high of 43 in 1995 to a low of 24 in 2002. It also shows that although this percentage had generally declined since 1995, it increased from 2002 through 2004.

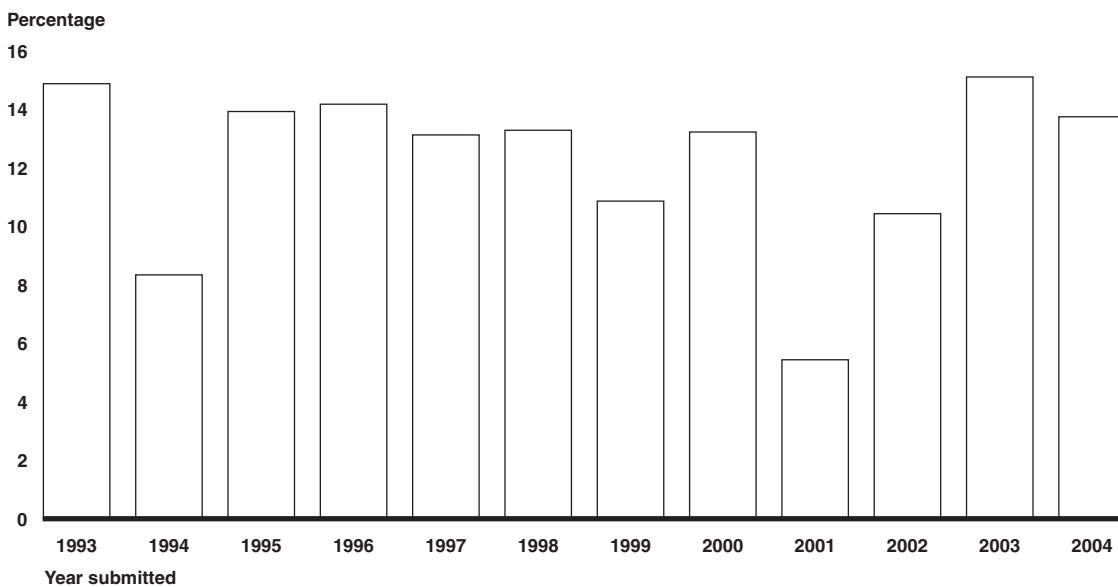
Figure 6: Percent of NDAs Submitted that were NMEs, 1993-2004



Source: GAO analysis of FDA data.

Regarding priority NMEs, figure 7 shows that in general, the percentage of NDAs that were priority NMEs ranged from between 10 and 15 percent during the 12-year period. Figure 7 also shows that this percentage ranged from a high of 15 in 2003, to a low of 5 in 2001. Finally, it shows that after a steep reduction in 2001, this percentage increased the following 3 years to levels similar to those previously experienced.

Figure 7: Percent of NDAs Submitted that were Priority NMEs, 1993-2004



Source: GAO analysis of FDA data.

The results of our analyses indicate that the reported increases in research and development expenditures during the period have not led to a commensurate increase in the innovative potential of NDAs submitted to FDA. These findings are consistent with FDA’s conclusions in its 2003 and 2004 reports. In its January 2003 report on improving innovation in medical technology—including drugs—FDA found that data regarding application submissions showed a trend toward decreased numbers of applications for truly innovative products, including NMEs.²³ The report also concluded that the trends were of concern to FDA because at the same time, it had seen a substantial increase in the number of applications for new products, including new drugs in areas where comparable products already existed—such as non-NME NDAs. Further, these same trends, which suggested stagnation in innovation, were noted as a basis for FDA’s launch of the critical path initiative in 2004.

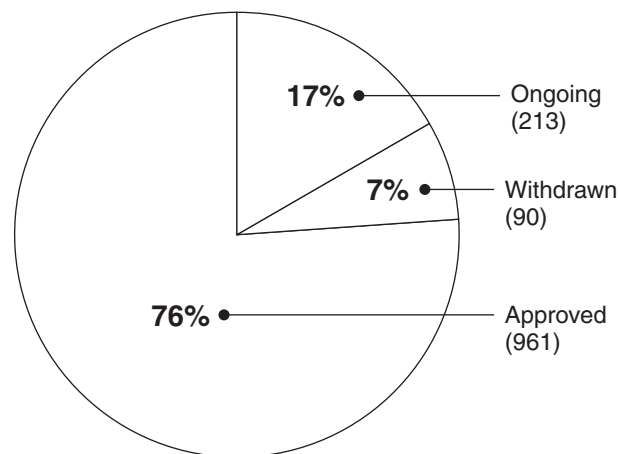
²³FDA, *Improving Innovation in Medical Technology: Beyond 2002* (Jan. 31, 2003).

FDA Approves Most NDA Submissions, and Approval Times Have Been Decreasing

We reviewed the status of all 1,264 NDAs submitted from January 1, 1993, through December 31, 2004, to determine approval trends. Our review found that as of September 2005, FDA had approved 961, or 76 percent of the NDAs submitted. Further, we found that FDA approval times have been decreasing and that approval times were consistently shorter for priority NDAs. We also found that most of the NDAs approved from 1993 through 2004 were for non-NMEs, or modifications to drugs already on the market. Finally, reflecting the declining number of NDA submissions, we found that the numbers of NDAs and NMEs approved each year have generally been declining.

The status of the 1,264 NDAs as of September 2005, shown in figure 8, indicates that FDA had approved the majority of them, and the remaining were either still under FDA review or had been withdrawn by the sponsors.

Figure 8: Status as of September 2005 for the 1,264 NDAs Submitted, 1993-2004



Source: GAO analysis of FDA data.

In addition to determining the overall approval rate over the period, we calculated approval rates for each year the NDAs were submitted. We found that approval rates were consistently above or near 80 percent for years 1993 through 2000. Approval rates for the later 4 years—and years 2003 and 2004 in particular—were lower because many of the NDAs

submitted—34 of the 106 submitted in 2003 and 51 of the 102 submitted in 2004—were still under FDA review at the time of our analyses.²⁴

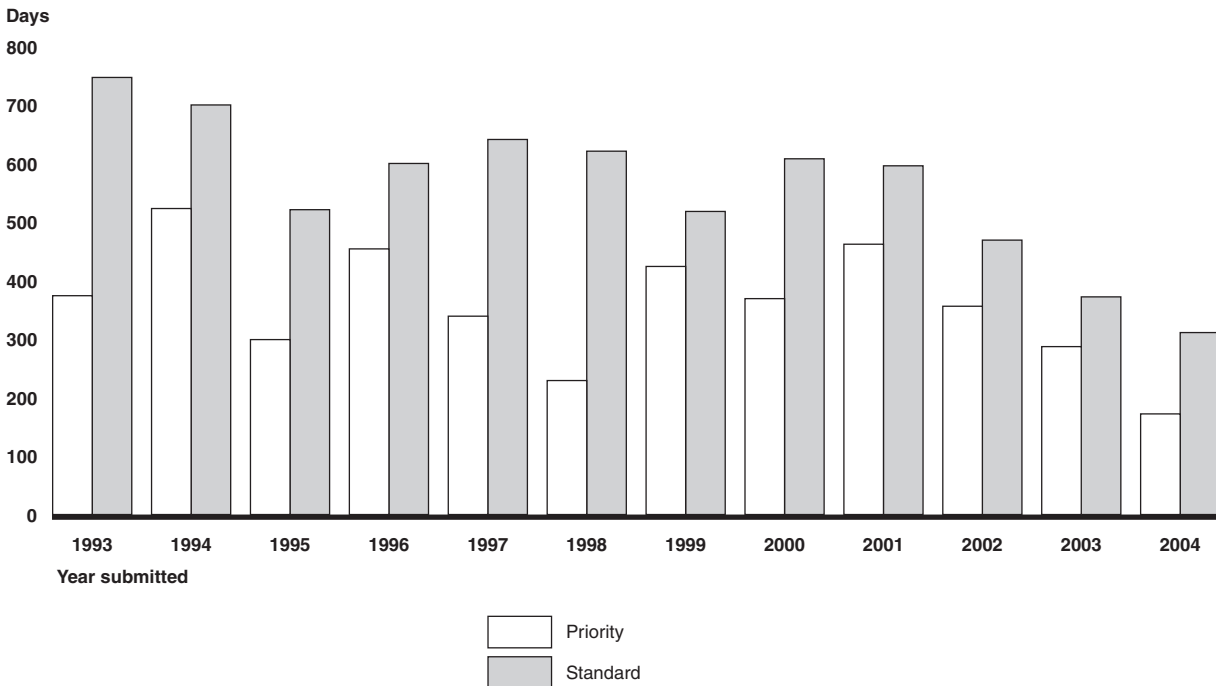
We also calculated the length of time it took FDA to approve each of the 961 NDAs, and determined the trends in average approval times based on the year the NDAs were submitted. Our analysis showed that the average time it has taken FDA to approve NDAs submitted in recent years is generally lower than for those submitted in earlier years. For example, we found that it took FDA, on average, 669 days to approve NDAs submitted in 1993, but only 442 days to approve those submitted in 2002—a 34 percent decrease.²⁵ This decrease is due, in part, to the fact that FDA has been approving an increasing number of NDAs in one or two review cycles, which has helped cut overall approval times.

Additionally, we found that approval times for priority NDAs were consistently lower than for standard NDAs. This was due, in part, to the fact that for those priority NDAs approved, FDA approved 63 percent of them in one review cycle, compared to 46 percent for the standard NDAs. Figure 9 shows the average approval times for priority and standard NDAs based on the year they were submitted, from 1993 to 2004. It should be noted that PDUFA was in effect during the period covered in figure 9. During that time FDA collected user fees and was subject to PDUFA performance goals.

²⁴FDA provided us with this information in September 2005. Therefore, many of the NDAs submitted in 2003 and 2004 were still under review at the time of our analyses.

²⁵Because many of the applications submitted during 2003 and 2004 were still under review at the time we performed our analyses, the average approval times for these years are artificially lower. Therefore, we did not use average approval times for these years to make any comparisons to earlier years.

Figure 9: Average Approval Times as of September 2005 for 961 Priority and Standard NDAs Submitted and Approved, 1993-2004



Source: GAO analysis of FDA data.

Note: NDA approval times include the time taken by FDA to review the application as well as time needed by the sponsor to address FDA's concerns. In addition, 85 of the 208 the applications submitted in 2003 and 2004 were still under review at the time of our analyses, and thus average approval times for these years may increase if they are eventually approved.

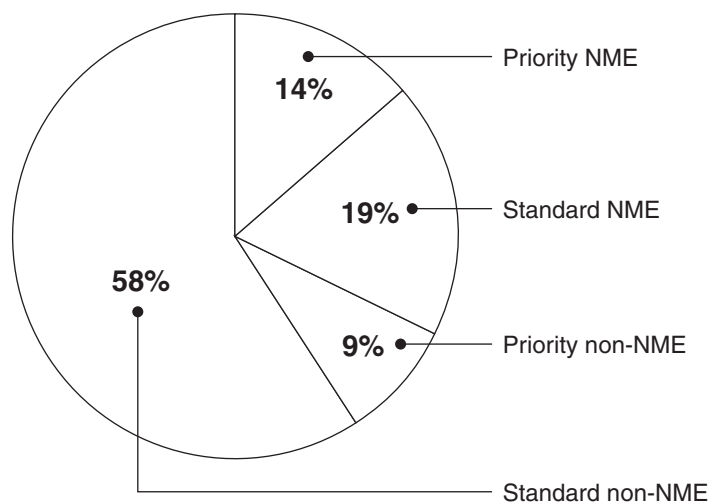
Previous studies have indicated that implementation of PDUFA's user fees and performance review goals have been a contributing factor to the quicker review times. For example, in 2002, we reported that fees collected under PDUFA had provided FDA with additional resources that have helped the agency expedite the approval of new drugs by reducing review times.²⁶ In addition, an October 2000 study by the Tufts Center for

²⁶GAO, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, [GAO-02-958](#) (Washington D.C.: September 17, 2002).

the Study of Drug Development concluded that user fees contributed to a 51 percent drop in average approval times from 1993 through 1998.²⁷

To categorize the innovative potential of the drugs submitted and approved during the period, we applied the same four-level ranking scale discussed earlier to the 961 NDAs that FDA approved. Based on our analysis, we found that, similar to the submission trends, most of the NDAs approved were for non-NMEs. Figure 10 shows the proportion of the NDAs categorized by innovative potential.

Figure 10: Proportion of 961 NDAs Submitted and Approved by Innovation Potential



Source: GAO analysis of FDA data.

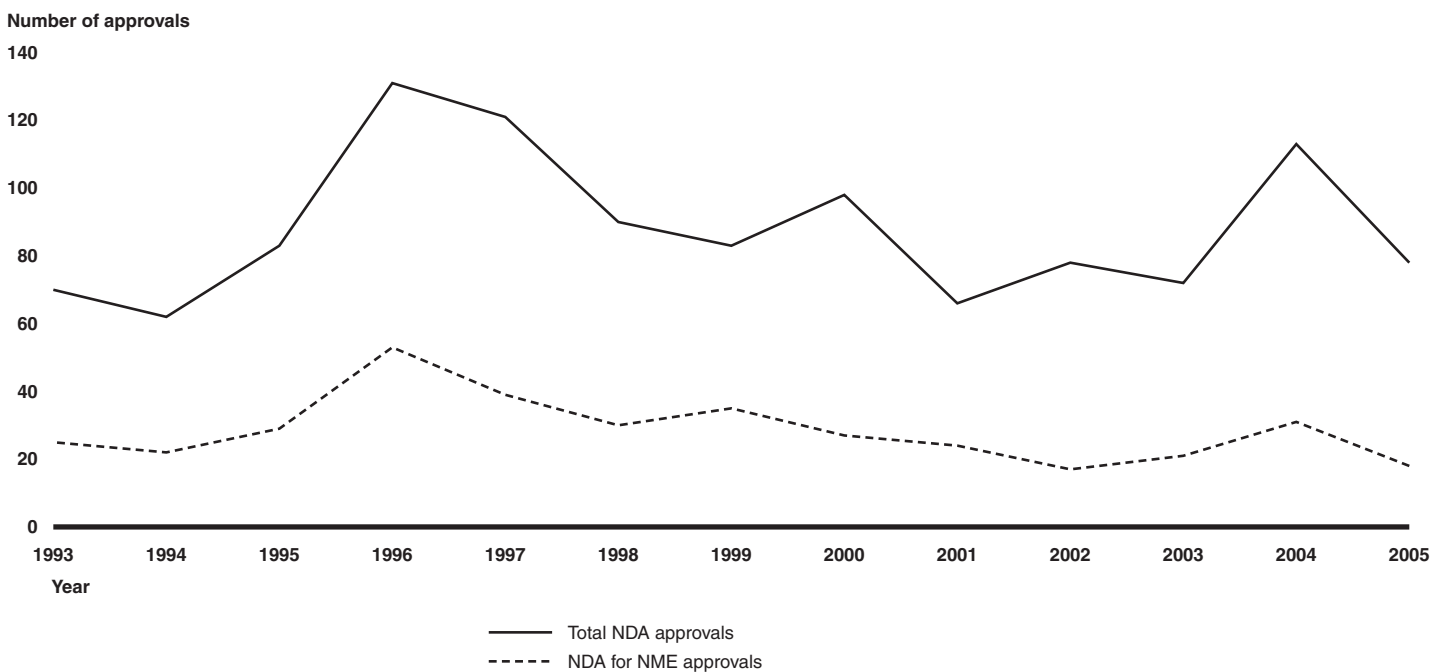
We also obtained historical data on the numbers of NDAs overall, as well as NDAs for NMEs that FDA has approved regardless of when they were submitted.²⁸ In doing so, we reviewed FDA's published data on its annual approvals of NDAs, including NDAs for NMEs for the years 1993 through

²⁷Tufts Center for the Study of Drug Development, *Impact Report, Analysis and Insight into Critical Drug Development Issues*, Vol. 2 (October 2000).

²⁸These data reflect the total number of NDAs and NDAs for NMEs approved annually from 1993 through 2005, and are used to show trends in the numbers of NDAs and NDAs for NMEs FDA approved during those years.

2005.²⁹ Figure 11, which is based on these data, shows that FDA approved an increasing number of NDAs and NDAs for NMEs from 1993 through 1996. After that time, however, reflecting the declining number of NDA submissions, annual approvals declined, and returned to levels not seen since the early 1990s. Also, there was a spike in the number of approvals in 2004, but approvals were lower once again in 2005.

Figure 11: Total NDA and NDA for NME Approvals, 1993-2005



Source: GAO analysis of FDA data.

²⁹FDA Center for Drug Evaluation and Research, *1997 and 2004 Reports to the Nation, Improving Public Health Through Human Drugs*, and FDA's 2005 new drug approval listings on its Web site (<http://www.fda.gov/cder/rdmt/ndaaps05cy.htm> downloaded March 3, 2006 and <http://www.fda.gov/cder/rdmt/nmecy2005.htm> downloaded March 3, 2006).

Experts Identified Factors Contributing to Declining Productivity in Drug Development and Offered Suggestions for Improvement

According to experts, a variety of factors have contributed to the declining productivity of pharmaceutical research and development efforts by making it more difficult for the industry to successfully complete clinical testing and submit NDAs for approval. These factors include limitations on the scientific understanding of how to translate chemical and biological discoveries into safe and effective drugs, business decisions by the pharmaceutical industry, uncertainty regarding regulatory standards for determining whether a drug should be approved, and intellectual property issues, such as the length of patent terms. According to experts, these factors have impacted the length, costs, and failure rates of drug development, as well as the innovative potential of NDAs being submitted to FDA. Although experts agreed that declining productivity may be a cyclical occurrence that will ultimately be reversed, they also acknowledged that they need to address the recent increase of clinical trial failure rates—from 82 percent during the period 1996 through 1999, to 91 percent during the period 2000 through 2003. As a result, they have proposed suggestions to expedite drug development and improve the overall productivity of research and development efforts.

Lack of Scientific Understanding in Treating Diseases Contributes to Increased Failure Rates and Increased Research and Development Expenditures

We found a general consensus that difficulties in effectively translating basic research discoveries into new and effective medicines have contributed to increased failure rates during clinical testing. In turn, this has led to increased costs of drug development. Difficulties in understanding the science of disease have historically challenged researchers. However, according to experts, these difficulties have been growing over the past several years as the volume of drugs in clinical trials and the complexity of the diseases to be addressed have increased. As a result, the inability of drug sponsors to consistently predict the efficacy of compounds, including those for complex diseases, has resulted in an increasing number of clinical failures and overall development costs. In addition, the inability of drug sponsors to effectively utilize new technologies and a shortage of highly trained researchers who possess the ability to effectively translate basic discoveries into new drugs, were seen as factors that further contribute to the increased clinical failures and costs.

During the panelists' discussion, it was generally agreed that the inability to effectively predict which compounds will be successful when tested in humans, combined with the greater numbers of compounds in clinical testing, have contributed to the increased number of drugs failing clinical testing and rising expenditures. Panelists commented that compounds which were thought to be effective treatments during preclinical testing in

animals can ultimately fail when tested in humans because available animal models used to estimate a compound's effectiveness have limited ability to predict whether they will be effective in treating humans.³⁰ This issue was also highlighted in a joint report issued by the Association of American Medical Colleges (AAMC) and FDA, which found that although animal models can be useful by providing biological insights, there is still a lack of understanding when it comes to extrapolating results from animal models to human studies.³¹

According to industry analysts, the pharmaceutical industry's increasing focus on developing drugs for complex and chronic diseases such as cancer has also contributed to higher failure rates, slower drug development, and increased costs. Because many of these diseases have not been fully studied, knowledge of how drugs impact relevant cells remains incomplete. For example, scientists have rarely been able to develop cancer therapies that exclusively eliminate cancer cells without also destroying healthy tissues. As a result, many cancer drugs have failed in clinical testing because of adverse side effects. Analysts have noted that in order to document the safety and efficacy of drugs used to treat complex and chronic diseases, longer studies with larger patient populations are required, which increases both development time and costs. Similarly, analysts reported in 2003 that therapies for complex and chronic conditions are generally more costly to test, as they typically require more complex patient care and longer monitoring periods.³²

Over the past decade, new technologies including genomics and high-throughput screening have provided tools for researchers to discover and test compounds.³³ According to industry analysts, the use of these

³⁰For example, a panelist who was an industry representative explained that his company had compounds in development that were intended to affect the central nervous system and which successfully entered the brains of animals during preclinical testing. However, after testing the drugs in clinical trials—at a cost of \$10 to \$12 million a study—researchers found that the drugs did not enter the brain in humans.

³¹The Association of American Medical Colleges, Food and Drug Administration, Center for Drug Development Science at the University of California San Francisco, *Drug Development Science: Obstacles and Opportunities for Collaboration Among Academia, Industry and Government* (January 2005).

³²Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs", *Journal of Health Economics*, Vol. 22 (2003).

³³Genomics is used to study how various genes interact with drug compounds, and high-throughput screening allows researchers to conduct hundreds of tests at once through a combination of modern robotics and other specialized laboratory hardware.

technologies has led to increasing expenses without a commensurate increase in the number of drugs developed. These analysts have found that although companies have invested substantial resources in acquiring technologies that have generated vast quantities of newly discovered biological data, company researchers are still learning whether the data will lead to potentially valid drug candidates, resulting in compounds and drugs that have failed in either preclinical or early clinical testing. While the panelists generally agreed that the productivity of the pharmaceutical industry is currently declining, they stressed that this trend may be part of a cycle that will reverse itself, as researchers improve their ability to exploit these technologies.

Furthermore, a shortage of physician-scientists, also known as translational researchers—who possess both medical and research degrees and thus the expertise needed to translate discovery-stage research into safe and effective drugs—was seen by panelists and other experts as a fundamental barrier to increasing the productivity of drug development. During the panel discussion, it was generally agreed that a shortage of translational researchers was a key factor contributing to the declining productivity of pharmaceutical research and development efforts, particularly with the increasing use of new technologies and the shift in research focus to more complex diseases. In addition, analysts have reported on this decline, and cited research which found that the number of physician-scientists declined by 22 percent from 1983 to 1998.³⁴ Experts attribute this shortage to a variety of factors, including lengthy training and relatively lower compensation for physicians who are scientists, compared to those in clinical practice. In addition, researchers, including those in academia, have noted that academic institutions have not taken the initiative to provide financial incentives, such as scholarships, for medical students to pursue these research interests.

The Business Environment Drives Drug Development Decisions

Experts generally agreed that business considerations greatly influence the industry's priorities of what drugs to pursue. The conflicting pressures of avoiding risk and producing a high return on investment, in addition to the recent mergers of pharmaceutical companies, have shaped business decisions and affected productivity.

³⁴See, for example, Ajit Varki and Leon E. Rosenberg, "Emerging Opportunities and Career Paths for the Young Physician-Scientist", *Nature Medicine*, Vol. 8, No. 5 (May 2002).

Over the past 10 years, the trend in the pharmaceutical industry has been to focus on developing drugs that produce a high return on investment, which has reduced the numbers and types of drugs produced. This strategy has led pharmaceutical companies to pursue development of blockbuster drugs, which are usually for large patient populations and have the potential to reach \$1 billion in annual sales. Blockbuster drugs may be developed to the exclusion of other drugs for more limited populations that generate much less revenue. Drug development experts and several panelists reported that companies frequently choose to stop developing drugs that do not offer the same revenue-generating potential as blockbuster drugs, even though they could be highly innovative and offer therapeutic advances. According to an industry consultant we contacted, pharmaceutical companies have annual sales thresholds in place which play a key role in determining which drugs to continue developing.³⁵ The emphasis on developing blockbuster drugs has been highlighted by numerous industry analysts, who have noted that the number of blockbuster drugs being sold has more than doubled over the past several years. This strategy can also diminish the amount of resources available to develop therapies to treat more limited patient populations and less visible diseases.³⁶ Due to increased competition among companies, the blockbuster strategy has also been cited as a factor leading to increased costs from late-stage development failures. According to researchers we interviewed from the Tufts Center for the Study of Drug Development, although companies have pursued drugs that they believed had huge market potential, they later discovered that the potential for substantial revenue no longer existed for some of these drugs because competitors had already begun marketing similar drugs. Tufts researchers stated that such companies subsequently discontinued production of what they thought would be blockbuster drugs, and that often times these decisions were made late in Phase 3—the most complex and costly phase—and thus companies discontinued development after incurring substantial costs.

³⁵For example, the industry consultant indicated that because shareholders expect large companies to develop drugs that produce revenues of at least \$200 to \$500 million per drug per year, they frequently stop the development of drugs not expected to meet this threshold.

³⁶Congress provided incentives to expedite the development of drugs for rare diseases with the enactment of the Orphan Drug Act in 1983, such as tax credits for clinical testing expenses. 26 U.S.C. § 45C. Although companies have been producing drugs under these provisions, the panelists noted that, in certain instances, the industry does not view these incentives as sufficient to encourage development.

Industry analysts have also reported that with increased development costs and complexity, and with more competition, companies prefer to produce drugs that require little risk taking but still offer the potential for high revenues. This strategy has created an emphasis on producing “me too” drugs—drugs which have a very similar chemical formulation to drugs already on the market. These drugs are less risky to develop because the safety and efficacy of the drugs on which they are based have already been studied. According to one panelist, an industry representative, because the length, complexity, and expense of developing a single drug have all increased dramatically over the last 10 to 15 years, companies must choose fewer drugs to develop. As a result, they will often follow a business model that involves choosing drugs that are easy to develop, with a large market that will produce a large return on investment.

Some experts and analysts who are critical of the pharmaceutical industry often state that the emphasis on “me too” drugs reduces innovation because such drugs do not offer any significant therapeutic benefits over products already being sold.³⁷ For example, they state that companies have produced different drugs all designed to combat depression or reduce cholesterol, and that such “me too” drugs have similar therapeutic benefits. As a result, these critics assert that this strategy diverts resources from developing drugs that offer greater innovative potential. However, industry analysts report that “me too” drugs benefit consumers by offering alternative and safer therapies. For example, they indicate that the side effects and efficacy of these drugs can vary from person to person, which gives physicians more options in treating their patients. In addition, analysts report that “me too” drugs increase competition, which can lower the price of drugs in the market.

Another major business strategy that has affected the success of drug development since the early 1990s is mergers and acquisitions in the pharmaceutical industry.³⁸ According to industry analysts, the industry pursued mergers and acquisitions because it anticipated it would increase the productivity of research and development. Instead, they noted that

³⁷For example, see Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* (Random House, 2004).

³⁸A merger occurs when two firms agree to combine and form a single new company. An acquisition occurs when one company purchases another company and establishes itself as the new owner. Examples of some of the largest mergers and acquisitions include Astra with Zenica (1999), Glaxo Wellcome with SmithKline Beecham (2000), and Pfizer with Pharmacia (2003).

with the rise in research and development costs, the newly formed company often reviews its combined inventories of potential products and selects only the most promising compounds for further development. For example, after consolidating their research efforts, the company may choose to discontinue one of the individual company's previous research areas because the projected financial benefits of the product lines fail to meet the new company's revenue expectations. In addition, analysts have found that mergers and acquisitions may also result in additional pressure to develop a blockbuster drug because investors expect the combined company to generate a substantial growth in revenue. According to a summary of a winter 2002-2003 Tufts survey³⁹ of 35 clinical research organizations, merger and acquisition activity was cited as a large barrier to drug development.⁴⁰ Due to mergers and acquisitions, nearly 50 percent of these organizations reported that drug development projects were cancelled during the 2 years prior to the survey, and that 90 percent experienced project delays.

Factors in the Operating Environment Affect Drug Development Outcomes

Based on the results of discussion among panel members, our interviews with drug development experts, and our review of prior studies, we identified several other factors that affect the numbers, types, and costs of drugs being developed. These factors affect the operating environment in which drug sponsors make their decisions, and play a role in shaping development priorities. They include sponsors' uncertainty over how they are to implement requirements for the safety and efficacy of new drugs, and the impact of intellectual property protections on pharmaceutical innovation.

Regulatory Uncertainty Can Hamper Drug Development

We found that uncertainties regarding regulatory requirements concerning both drug safety and effectiveness can impact the success of drug development efforts. During the panel discussion, there was general agreement that the lack of precise FDA regulatory standards that outline what constitutes a safe and effective drug is a factor when making drug development decisions—weighing the safety of drugs against their

³⁹Tufts Center for the Study of Drug Development, *Impact Report*, Vol. 5, No. 4 (July/August 2003).

⁴⁰Clinical research organizations contract with drug sponsors to implement aspects of clinical trials, such as the design of a protocol, selection or monitoring of investigations, evaluation of reports, site monitoring visits, statistical analysis, and preparation of reports to FDA.

potential therapeutic benefits. Panelists generally agreed that because there are no precise standards for making these decisions, sponsors and FDA must address them on a case-by-case basis. As a result, it was indicated that this uncertainty may lead a drug sponsor to abandon a drug rather than risk significant development expenditures. Panelists also indicated that this uncertainty creates risk-averse behavior that can reduce the prospects for innovative therapies. During the panel discussion and interviews, FDA officials acknowledged that the regulatory standards are not precise and that it needs to have flexibility to address safety and efficacy issues as they arise. For example, FDA officials stated that they may discover a new drug-to-drug interaction that could affect the safety risks of an NDA under review, and in such a case, they would utilize the new information to address previously unknown safety issues.

We also identified a perception held by some drug development experts and industry analysts that FDA, in response to several events involving drug safety, has increased its review requirements during the drug development process. Some analysts believe that these increased review requirements have contributed to the increased time and costs of drug development by requiring more complex and costly studies. Some analysts have reported that safety concerns during the 1990s—which led FDA to request that manufacturers withdraw pharmaceuticals including fenfluramine and dexfenfluramine (known as Fen-Phen) in 1997, Propulsid and Rezulin in 2000, and Baycol in 2001—impacted FDA’s review requirements.⁴¹ For example, a 2004 report completed for the European Commission—the executive body of the European Union—found that the withdrawals of these pharmaceuticals from the market affected FDA’s implementation of its regulatory standards.⁴² According to this study, FDA began to demand more complex clinical trials that called for more testing on: (1) how drugs interact with each other, (2) the effect of drugs on liver toxicity, and (3) the relationship of drugs to cardiac risk. In addition, according to several drug development experts and some industry analysts, FDA has been requiring more lengthy and complex clinical trials, which call for more patients and increased costs. For example, according to one analysis, the average number of patients participating in clinical

⁴¹Propulsid and Fen-Phen were withdrawn due to increased risk of potentially fatal heart problems; Rezulin was withdrawn due to increased risk of liver failure; and Baycol was withdrawn due to increased risks of potentially fatal muscle damage.

⁴²*Innovation in the Pharmaceutical Sector, a Study Undertaken for the European Commission* (Charles River Associates, London: November 2004).

trials per NDA increased by 19 percent during the period 1995 to 2001, as compared to the period 1990 to 1994, due, in part, to increasing federal regulations.⁴³ In its comments on a draft of this report, HHS acknowledged that FDA may be increasing data requirements in some instances. However, it stressed that in many cases, the increase in the amount of data submitted results from a sponsor's decision to provide support for new claims or to better position its product relative to existing products.

Our review of studies and interviews with several experts revealed that there is a lack of consensus among FDA, industry, and academia as to what can constitute a valid measurement for proving the effectiveness of drugs for many diseases. As a result, these sources indicate that drug development can be more complex, lengthy, and costly than necessary, because drug sponsors are unsure how to demonstrate a drug's effectiveness. Drug sponsors rely on end points—or objective measurements—to evaluate effectiveness. Clinical end points demonstrate the effectiveness of a drug on a human, such as a medication that can be proven to prevent strokes. However, it can be easier to prove a drug's efficacy by using valid biomarkers as surrogate end points (e.g., showing a medicine is effective in reducing blood pressure instead of proving it will prevent strokes).⁴⁴ FDA has approved many drugs to treat the HIV/AIDS virus using surrogate end points. However, due to the uncertainty among FDA, industry, and academia over when it is appropriate to use surrogate end points, expanding their use has been difficult, and has been recognized by FDA as one issue that needs to be addressed. For example, in its March 2004 paper outlining the critical path initiative, FDA concluded that adopting new biomarkers and surrogate end points for effectiveness standards can drive rapid clinical development, and that efforts are needed to develop them to help guide drug development.⁴⁵ This issue was also extensively addressed in the joint report issued in 2005 by

⁴³B. Hirschhorn, *Understanding the Development of the Clinical Study Budget While Avoiding Bumps and Pitfalls* (Temple University, Philadelphia, Pa.: 2004).

⁴⁴A biomarker is a physical characteristic that can be objectively measured, such as blood pressure. A surrogate end point is a laboratory measurement or a physical sign that can predict the effect of a medicine on a disease. In 1992, FDA issued regulations that allow for the accelerated approval of new drugs for serious or life-threatening diseases based on surrogate end points that are reasonably likely, based on scientific evidence, to predict clinical benefit. 21 C.F.R. § 314.510.

⁴⁵FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004).

Intellectual Property
Protections Have Affected Drug
Development

FDA and the AAMC in response to FDA's critical path initiative.⁴⁶ That report identified a need to clarify guidance governing the level of evidence required to support the use of biomarkers and surrogate end points. In March 2006, FDA published a report outlining six areas to help increase productivity in drug development.⁴⁷ One of these areas included developing new biomarkers which, according to FDA, could increase the safety of new drugs, reduce the costs of clinical trials, and expedite drug development. According to FDA's senior manager for its critical path initiative, the agency is currently working with industry and academia to develop biomarkers and other tools to enhance the drug development process.

During our review, we found a wide variety of views among consumer advocates, drug development experts and analysts, and industry representatives regarding how the protection of intellectual property affects innovation in drug development. Intellectual property protections are designed to help encourage innovation by providing financial incentives to engage in research and development efforts.

One form of intellectual property protection is a patent, which provides its owner with the right to exclude others from making, using, or selling an invention for 20 years.⁴⁸ In the United States, the U.S. Patent and Trademark Office issues patents. Typically, companies that develop brand-name drugs obtain a patent on the active ingredient used in the drug. Patents are seen as playing a key role in drug development, because they allow pharmaceutical companies to charge prices that allow them to recover their investments made in discovering and developing a new drug and earn a profit. Drug manufacturers typically apply for patents for compounds while their medicinal properties are still being developed and evaluated. Therefore, the quicker companies are able to develop a new drug and receive market approval from FDA, the more time they have to sell their drugs without facing competition. The amount of patent

⁴⁶The Association of American Medical Colleges, Food and Drug Administration, Center for Drug Development Science at the University of California San Francisco, *Drug Development Science: Obstacles and Opportunities for Collaboration Among Academia, Industry and Government* (January 2005).

⁴⁷FDA, *Innovation or Stagnation, Critical Path Opportunities Report* (March 2006).

⁴⁸Traditionally, the length of patent terms was 17 years. This was amended to 20 years in 1994 with the enactment of the Uruguay Round Agreements Act. See 35 U.S.C. § 154 (a)(2).

protection remaining after receiving FDA market approval is known as the effective life of a patent.

Through both their reports and our interviews with them, consumer advocates and some pharmaceutical industry analysts expressed concerns that certain intellectual property protections do not encourage innovation.⁴⁹ First, they contended that companies can easily obtain new patents by making minor changes to existing products regardless of whether the drugs offer significant therapeutic advances. Second, they indicated that pharmaceutical companies may develop new uses for previously approved drugs that have no patent protection and receive an additional 3 years of “market exclusivity.”⁵⁰ According to these sources, these intellectual property protections enable companies to earn significant profits while reducing the incentive to develop more innovative drugs. These sources pointed to the relatively high percentage of non-NMEs, and standard NMEs in particular, that have been approved over the past decade as evidence that development efforts have focused on making changes to existing drugs. Some analysts specifically highlighted the practice commonly known as producing line extensions—deriving new products from existing compounds by making small changes to existing products, such as changing a drug’s dosage, or changing a drug from a tablet to a capsule. According to analysts, these changes are typically made to blockbuster drugs shortly before their patents expire. Some analysts also concluded that this practice redirects resources that otherwise could be applied to developing new and innovative drugs.

In contrast, the pharmaceutical industry contended that due to the rising costs and complexity of developing new drugs, these intellectual property protections are crucial to maintaining drug development efforts.⁵¹ Drug

⁴⁹For example, see National Institute for Health Care Management, *Prescription Drugs and Intellectual Property Protection, Finding the Right Balance Between Access and Innovation* (August 2000).

⁵⁰This protection was added to the Federal, Food, Drug, and Cosmetic Act with enactment of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Waxman-Hatch Act. Among other things, it bars FDA from approving an application to market a generic copy of certain drugs, for a 3-year period, if the clinical investigations relied upon by the applicant for approval were not conducted by or for the applicant, and the applicant has not been authorized to rely upon such studies. 21 U.S.C. § 355(c)(3)(E)(iii).

⁵¹For example, see PhRMA White Paper, *Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong and Predictable Intellectual Property Rights* (April 2002).

sponsors and industry analysts also indicated that new drugs produced by modifying existing compounds are the result of incremental innovation, and such drugs can result in important therapies. For example, by changing a medicine to reduce its dosage schedule requirements, some industry analysts indicated that patients are more likely to comply with their prescription's instructions. Finally, some analysts assert that the revenues generated from incremental innovation are needed to fund the more risky ongoing research and development efforts, which can lead to new innovations.

Drug Development Experts Offered Suggestions to Improve Productivity and Innovation

While panelists indicated that the productivity of drug development is currently in a downward cycle, and that the cycle would eventually reverse, they were uncertain when this would occur. Therefore, they recognized the importance of taking steps to develop and implement initiatives to increase the number, and innovative potential, of drugs being produced. To help accomplish this, the panelists and other experts—including representatives from the pharmaceutical industry, academia, public interest groups, and FDA—made a variety of suggestions to reduce the costs, increase the speed, and encourage innovation in drug development. While not every expert mentioned every one of the suggestions below, or ranked them in a particular order, we found that certain suggestions were highlighted in the panel's discussion, our interviews, and academic and industry reports as having the potential to improve the productivity of drug development. However, some of these experts also cautioned that any change that expedites the drug development process should be tempered with appropriate measures to ensure that safety is not compromised. These suggestions include:

- Collaborative efforts among the government, industry, and academia to:
 - Design a system to collect and analyze data on why drugs fail during clinical testing. For example, a team of FDA and pharmaceutical representatives could review FDA and company databases to obtain examples of drug failures and then perform a systematic analysis of the causes of these failures. This effort would need to ensure protection of each company's proprietary information on specific drugs. Such an effort may provide new information to prevent multiple companies from making the same or similar mistakes and may increase efficiency in clinical trials.
 - Develop inventories of validated biomarkers and surrogate end points to use when testing the safety and efficacy of drugs in development.

According to experts, to increase the utilization of validated surrogate end points, government, industry, and academia could also work together to clarify FDA's guidance and the level of scientific evidence needed to support the use of biomarkers and their validation as surrogate end points.

- Identify diseases in great need of treatment, and implement an expedited regulatory process using conditional approval to decrease the time needed to develop drugs to treat these diseases. According to experts, a new expedited process would require less detailed study and information and allow for more limited clinical trials. Therefore, experts said that an expedited process would help lower the cost of creating drugs for these diseases, and serve as an incentive to increase drug development for such diseases. To help ensure safety, the drugs would have conditional approval—they would initially be distributed to certain populations whose usage of the drug can be studied and carefully monitored before wider distribution would be allowed.⁵²
- Academia could place a greater emphasis on developing research scientists with knowledge of translational medicine by providing financial incentives, such as scholarships, for students to pursue this discipline. Private and public partnerships could also create these incentives to develop such scientists. One of the panelists suggested that academia, industry, and FDA formally develop a paper that describes the skills most needed by this new type of translational scientist and develop funding and training mechanisms that would specifically support these individuals.
- The federal government could consider providing financial incentives or disincentives to affect the innovative potential of drugs produced by the industry. The government could achieve this by extending or reducing the period of patent protection associated with a drug based on its therapeutic value. One of the panelists suggested that a patent could be extended to 25 or 30 years for drugs considered innovative, or offering high therapeutic potential; while patents for drugs offering less innovative benefits could be only 10 years.

⁵²Although FDA has an accelerated approval process for new drugs to treat serious or life-threatening conditions, the suggestion of the panelists was made in the context of broadening this process to accommodate other illnesses. Under the accelerated approval process, drugs designed to treat serious or life threatening conditions may be approved conditionally, that is, the applicant may be required to conduct further drug studies following approval to market the drug, to verify and describe the drug's clinical benefits. Applicants are also required to submit promotional materials to FDA during specific timeframes. 21 U.S.C. § 356; 21 C.F.R. §§ 314.510, 314.550.

Concluding Observations

Developing new drugs is complex, risky, and challenging. It is also important to the health and well-being of society, and can provide substantial financial rewards to companies. Recent trends reveal the number of drugs developed has not been commensurate with research and development investments by the pharmaceutical industry. While experts believe these trends are part of a cycle that can be reversed, there is no clear expectation of when the industry will become more productive—that is, producing greater numbers of new drugs, and more specifically, those representing significant therapeutic advances. The extent to which scientific, business, regulatory, and intellectual property issues related to drug development can be addressed will largely determine if and how quickly these trends can be reversed. Addressing this challenge will require effective collaboration between government, industry, and academic institutions.

Agency Comments

HHS provided comments on a draft of this report. HHS's comments appear in appendix III. Among its general comments, HHS officials stated that our ranking of the innovative potential of NDAs based on FDA's chemical type and therapeutic potential classifications was misleading. Specifically, HHS disagreed with our premise that an NDA classified as a standard NME should be ranked as more innovative than one classified as a priority non-NME. It noted classification as an NME is not necessarily commensurate with innovation and gave an example of a priority non-NME that could offer more therapeutic potential than a standard NME. We noted in our draft, that any one NDA—regardless of whether it is for an NME or was granted priority status by FDA—may eventually prove to be an innovative and uniquely therapeutic product. However, our discussions with FDA officials and our review of prior studies—including those conducted by FDA—revealed a general consensus that the most important factor in assessing the innovative potential of an NDA at the time of submission was whether or not it was an NME. For example, FDA has highlighted the declining number of NDAs for NMEs as an indicator of the stagnation of innovation. In its 2003 initiative, it reported a decline in the number of submissions of NDAs for NMEs in both the priority and standard classifications and noted this was an indication of decreases in the submission of applications for truly innovative new products.⁵³

⁵³See FDA, *Improving Innovation in Medical Technology: Beyond 2002* (Jan. 31, 2003).

HHS's general comments also noted that statutory changes may be needed to implement the experts' suggestion to expedite FDA's regulatory process by instituting a new system of conditional approval. Although we noted in the draft report that FDA has authority to issue conditional approvals for certain drugs to treat serious or life-threatening conditions under its current accelerated approval program, we agree that, depending on the specific parameters of any new system, statutory changes could be necessary.

Further, HHS's general comments included additional clarifications. For example, HHS expressed concern that our explanation of why FDA could only provide data on NDAs through 2004 could be misleading and imply that FDA is not good at tracking its data. In response, we clarified the report to reflect that FDA provided data on NDAs through 2004 specifically at our request, as this was the most recent year with a complete set of NDA submission data at the time our request was made. We also made other clarifications in response to HHS's general comments. In addition, HHS provided us with technical comments, which we incorporated throughout the report, as appropriate.

As agreed with your offices, we plan no further distribution of this report until 30 days after its date. At that time, we will send copies of this report to the Secretary of HHS, the Acting Commissioner of FDA, appropriate congressional committees, and other interested parties. We will also make copies available to others upon request. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staff has any questions, please contact me at (312) 220-7600 or at aronovitzl@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



Leslie G. Aronovitz
Director, Health Care

Appendix I: Scope and Methodology

To determine trends in the pharmaceutical industry's reported research and development expenditures, we obtained research and development expenditure information from the Pharmaceutical Research and Manufacturers of America (PhRMA). We obtained this information for the period 1993 through 2004, adjusted for inflation to 2004 dollars. We did not independently verify these expenditure data; however, many researchers have cited these data as the best available information, and they represented the best available information at the time of our study.¹

To determine the trends in the number of submissions and approvals of NDAs, we requested that the Food and Drug Administration (FDA) provide information on all 1,264 new drug applications (NDA) submitted to FDA from January 1, 1993, through December 31, 2004.² We chose this time period because it generally corresponds to changes FDA implemented to its process for reviewing NDAs. Specifically, in 1992, FDA implemented a new system for categorizing NDAs, using the priority and standard designations and in 1993, FDA implemented time-frame goals for reviewing NDAs. At the time we requested these data—July 2005—information through 2004 was the most current year for which FDA could provide complete data. We also compared the trends in the numbers of NDAs and NDAs for new molecular entities (NME) submitted to FDA to the trends in the research and development expenditures over the same 12-year time frame.

For each of the NDAs, we requested and obtained descriptive and status information—such as each NDA's unique number, its review designation (either priority or standard), whether it was for an NME, and all of the dates documenting when drug sponsors provided information to FDA and when FDA made decisions during the review and approval process. After receiving this information, we performed a series of data analyses to identify trends in the submission and approval of NDAs, and calculated approval time frames for the NDAs. In calculating approval time frames,

¹For example, see Kaiser Family Foundation, *Prescription Drug Trends*, (October 2004) and National Institute for Health Care Management, *Issue Brief, Factors Affecting the Growth of Prescription Drugs Expenditures* (July 1999).

²In addition to requesting information on NDAs, we initially requested information on applications for biological products, which are derived from living sources (such as humans, animals, and microorganisms) as opposed to being chemically synthesized. However, based on the data FDA provided, there were only 60 applications over the 12-year period. Therefore, we determined that it would not be meaningful to perform trend analyses on such a small number, and we limited the study's scope to NDAs.

we included both the time FDA spent reviewing the NDAs and any additional time needed by the sponsor to address any FDA review concerns.

In addition to obtaining data on the 1,264 NDAs submitted from January 1, 1993, through December 31, 2004, we obtained information from FDA on the number of NDAs and NDAs for NMEs the agency approved each year from 1993 through 2005. We used this information to analyze NDA and NDA for NME approval trends, regardless of the years these NDAs were submitted. We also obtained information from FDA on the number of investigational new drug applications (IND) filed with the agency each year from 1986 through 2005.³ We chose this time period for two reasons. First, because it takes 7 years, on average, to successfully complete clinical trials, trends emerging from INDs submitted in 1986 could be reflected in NDA submission trends beginning in 1993. Second, 2005 was the most recent year with complete data, and these IND data provided an indication of the productivity of research and development expenditures for the drug discovery and preclinical testing phases in more recent years.

We performed various tests of data reliability, including obtaining information about the data collection and management system and its controls that FDA uses to ensure the data are reliable, and corroborating the data by comparing them to other published information. Based on our work, we believe the data we used were sufficiently reliable for the purpose of our report.

To determine factors affecting new drug development, and to obtain experts' suggestions to expedite the process, we took several steps. First, we interviewed various experts from FDA, the pharmaceutical industry, health care organizations, a consumer group, and academia, who possess knowledge of issues that have had an impact on drug development. Specifically, we interviewed officials from FDA's Center for Drug Evaluation and Research and the Critical Path Institute—which was founded by FDA, the University of Arizona, and SRI International, an independent, nonprofit research institute. In addition, we spoke to experts from PhRMA and other pharmaceutical industry analysts, including an independent consultant to the pharmaceutical industry. We also

³There are two classes of INDs—commercial and noncommercial. Commercial INDs are submitted primarily by companies whose ultimate goal is to submit an NDA to obtain marketing approval for a new product. Noncommercial INDs are filed for noncommercial research purposes. In this report, all references to INDs refer to commercial INDs.

interviewed representatives from the American Medical Association, the Association of Clinical Research Organizations, and the National Institute for Health Care Management. Finally, we interviewed officials from Public Citizen, a consumer advocacy group, and experts at six academic institutions—Boston University, the University of California-Davis, the University of Medicine and Dentistry of New Jersey, the University of Minnesota, Tufts University, and Vanderbilt University. Second, we analyzed reports and articles by pharmaceutical industry financial analysts, academic researchers, consulting firms, and the federal government to obtain information regarding factors impacting drug development and potential solutions to address them.

To supplement information from our interviews and review of studies, we contracted with the National Academy of Sciences (NAS) to convene a balanced, diverse panel of experts. At our request, these experts discussed key factors accounting for the drug submission and approval trends from 1993-2004, factors impacting new drug development, and potential solutions that either the pharmaceutical industry, academia, or the government can take to enhance new drug development. We worked closely with NAS to identify and select potential panelists who represented industry, government, advocacy groups, and academia who could adequately respond to our questions about the drug development process as well as the FDA regulatory review process. In keeping with NAS policy, the panelists were invited to provide their individual views, and the panel was not designed to build consensus on any of the issues discussed. After the expert panel was conducted on January 27, 2006, in Washington, D.C., we analyzed a transcript of the panel's discussion to identify each expert's views on key questions. The views expressed by the panelists do not necessarily reflect the views of the organizations with which they were affiliated or the NAS. A list of the experts who participated in this panel is contained in appendix II. We also reviewed applicable laws and regulations as part of our work. We conducted our work from July 2005 through October 2006 in accordance with generally accepted government auditing standards.

Appendix II: National Academy of Sciences Expert Panel Participants

At our request, the National Academy of Sciences arranged an expert panel discussion of new drug development issues. The panel discussion was held on January 27, 2006, and the panelists and their affiliations as of the date of the panel are listed below:

Moderator:

Edward Holmes, M.D., Dean, School of Medicine, University of California, San Diego

Panelists:

Jerry Avorn, M.D., Professor of Medicine at the Harvard Medical School and Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital

Peter Corr, Ph.D., Senior-Vice President for Science and Technology at Pfizer Inc.

William E. Evans, PharmD., Director and Chief Executive Officer at St Jude Children's Research Hospital

Garret A. FitzGerald, M.D., Chair of the Department of Pharmacology and Director of the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania School of Medicine.

Elaine Gallin, Ph.D., Program Director of the Medical Research Program at the Doris Duke Charitable Trust

Peter K. Honig, M.D., Senior Vice-President of Risk Management at Merck Research Laboratories

John K. Jenkins, M.D., Director of the Office of New Drugs, Center for Drug Evaluation and Research at the Food and Drug Administration (FDA)

David Korn, M.D., Senior Vice-President for Biomedical and Health Sciences Research at the Association of American Medical Colleges

Jeffrey Leiden, M.D., Ph.D. President & Chief Operating Officer of the Pharmaceutical Products Group at Abbott Laboratories

John Marler, M.D., Associate Director for Clinical Trials at the National Institute of Neurological Diseases and Stroke at the National Institutes of Health

Musa Mayer, author, breast cancer survivor, patient advocate, patient representative to the FDA's Oncologic Drugs Advisory Committee, and patient consultant to the FDA's Cancer Drug Development Program

Suzanne Pattee, J.D., Vice-President of Public Policy & Patient Affairs at the Cystic Fibrosis Foundation

Cecil Pickett, Ph.D., President of the Schering-Plough Research Institute

Appendix III: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

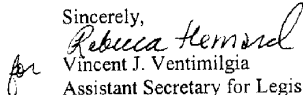
OCT 20 2006

Leslie G. Aronovitz
Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Aronovitz:

The Department of Health and Human Services has reviewed the U.S. Government Accountability Office's (GAO) draft report entitled, "NEW DRUG DEVELOPMENT: Science, Business, Regulatory and Intellectual Property Issues Have Hindered Drug Development Efforts"(GAO 07-49) and is providing general and technical comments. We look forward to working with GAO on these issues.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

for Vincent J. Ventimiglia
Assistant Secretary for Legislation

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED, "NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY AND INTELLECTUAL PROPERTY ISSUES HAVE HAMPERED DRUG DEVELOPMENT EFFORTS."
(GAO 07-49)

HHS Comments

Under "What GAO Found" on the summary page, the second to last sentence in the first full paragraph beginning on page 4, and the second sentence of the first paragraph on page 21, reference is made to FDA approving about 80% of the NDAs submitted. The concept is true, but it is not clear enough that that is an "eventual" outcome and not the "initial" (i.e., first cycle outcome). FDA recommends that it be clarified that FDA eventually approves about 80% of the NDAs submitted. Additionally, actual data show 76% approval of the NDAs submitted.

On page 3, footnote 4 explains why FDA was only able to give GAO all of the data for the cohorts through 2004 for the report. The explanation there could be misleading and lead some to conclude that FDA simply is not very good at tracking. It should more clearly explain that 2004 was the most recent submission cohort where all the applications had gone through at least one review cycle by the time of the data request.

On page 9, the criteria for priority review are paraphrased. Actual criteria should be cited rather than paraphrased. The first complete sentence on page 9 should be changed to read as follows: "Because a new molecular entity is considered an active moiety that has not previously been approved (either as the parent compound or as a salt, ester or derivative of the parent compound) in the United States for use in a drug product either as a single ingredient or as part of a combination, industry analysts and FDA generally consider them innovative."

On page 9, characterization of standard NDAs as "those with little or no therapeutic potential" is misleading. For example, a new 'statin' would probably be a standard unless they had data showing they were superior on a critical endpoint, even though it likely has the same therapeutic potential as other statins, which is very large.

On page 11, in the first full paragraph, characterization of what may be a resubmission to an NDA should note that the resubmission often contains new data (studies) to address FDA concerns.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED, "NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY AND INTELLECTUAL PROPERTY ISSUES HAVE HAMPERED DRUG DEVELOPMENT EFFORTS."
(GAO 07-49)

On page 17, Table 1 is misleading. NDA reviews are ranked on the potential innovation of new products based on our chemical and priority coding. FDA does not agree that a standard NME should be ranked as more innovative than a priority non-NME. A standard NME could be the new statin mentioned previously, while a priority non-NME could be a new delivery system for an already approved drug that makes the product much more effective or safe or significantly improve compliance. Being an NME in and of itself does not mean innovation. Even with respect to the chemical nature of an NME, often the NME is simply a minor modification to an existing product, or it can even be a prodrug of an already approved product. The order of NDA submission types should be ranked from most innovative to least innovative in the following order:

Priority NME
Priority non-NME
Standard NME
Standard non-NME

On pages 32-33, the report suggests that FDA is increasing the data requirements for approval, and that FDA are also asking for longer more complex trials. For some disease states, this may be true, but in many cases the increased amount of data submitted in the NDA is actually driven by the sponsor in order to support new claims or to better position their product relative to existing products. Balancing information should be included to clarify that it is not just FDA requests and requirements that can increase the size of applications.

On page 5, in the first full paragraph, line 15, GAO references a suggestion to expedite the drug review process by "restructuring regulation of the drug review process to allow for conditional approval of drugs for therapeutic areas that currently lack effective treatments based on shorter clinical trials using fewer numbers of patients..." Implementing such a suggestion might (would?) require statutory change

On page 9, first paragraph, lines 9-10, the phrase "Those with little or no therapeutic potential, compared to existing products..." should be changed to read "Those with no substantial therapeutic difference from existing products..."

On page 10, first paragraph, lines 5-6, the phrase "...completing its review of applications..." should be changed to read "...completing its review of a certain percentage of applications."

On page 38, the first full bullet references a suggestion to implement an "expedited regulatory process using conditional approval to decrease the time needed to develop" new drugs. FDA would need statutory change for this proposed expedited process.

3

Appendix IV: GAO Contacts and Staff Acknowledgments

GAO Contact

Leslie G. Aronovitz, (312) 220-7600 or aronovitzl@gao.gov

Acknowledgments

In addition to the contact named above, Geraldine Redican-Bigott, Assistant Director; Shirin Hormozi; Julian Klazkin; David Lichtenfeld; and Stephen Ulrich made major contributions to this report.

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