United States General Accounting Office

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Report to the Chairman, Human Resources and Intergovernmental Relations Subcommittee, Committee on Government Operations, House of Representatives

July 1994

FDA USER FEES

Current Measures Not Sufficient for Evaluating Effect on Public Health

GAO/PEMD-94-26

GAO

United States
General Accounting Office
Washington, D.C. 20548

Program Evaluation and
Methodology Division

B-253555

July 22, 1994

The Honorable Edolphus Towns
Chairman, Human Resources and Intergovernmental
Relations Subcommittee
Committee on Government Operations
House of Representatives

Dear Mr. Chairman:

In October 1992, the Congress passed the Prescription Drug User Fee Act of 1992 (Public Law 102-571). This law authorizes the Food and Drug Administration (FDA) to charge fees for reviewing new drug applications (NDAs) to determine whether the drugs can be marketed in the United States. The fees collected are to be used to augment FDA resources devoted to reviewing NDAs. This increase in resources, in turn, is intended to expedite review and approval. The ultimate goal of the user fee act is to improve the public health by allowing safe and effective new drugs to be made available to patients earlier.

Among the specifications of the act is a requirement that FDA annually provide data to the Congress. In this report, we respond to your request to examine this reporting requirement. Specifically, our focus is on whether the data mandated by the act will be sufficient to evaluate how well the act has achieved its goal of getting drugs to patients sooner.

First, we provide some brief background information about the drug review and approval process and about the user fee act. (A more detailed description of the process is in appendix I.) Then we describe the objectives, scope, and methodology of our study and conclude with our findings and recommendations.

Background

The Review and Approval Process for New Drugs

Before marketing a new drug in the United States, the sponsor must obtain approval from FDA. To receive approval, the sponsor must demonstrate that the drug is both safe and effective for its intended use. It is the sponsor's responsibility to assemble all the evidence concerning the drug's safety and efficacy and supply it to FDA in an NDA. It is then the agency's

responsibility to conduct a comprehensive review of the NDA and to make decisions regarding the marketing of the drug.

The process of reviewing and approving an NDA is complex and resource intensive. For years, there has been debate over whether approval takes too long.[1] Some critics have argued that the lengthiness of the process unnecessarily delays the availability of important new drugs. Other critics have argued that rushing the process allows unsafe or ineffective drugs onto the market.

The Prescription Drug User Fee Act of 1992

Joining the ongoing debate about whether FDA takes too long to approve new drugs, the Congress determined that "the public interest is served by more rapid approval of safe and effective drugs" and passed the Prescription Drug User Fee Act of 1992 to "provide the FDA with sufficient additional resources to significantly expedite the drug approval process." The expectation for the legislation was that "patients will have access to new drug therapies much sooner."

The user fee act gives FDA the authority to assess three kinds of fees: (1) a one-time fee for the submission of a human drug application, (2) an annual fee for each prescription drug product being marketed, and (3) an annual fee for each establishment manufacturing prescription drugs. The act establishes the amount of the fees, a schedule of increases through fiscal year 1997, authority to adjust the fees to reflect inflation, and the manner in which the fees are to be assessed and collected, and it stipulates that the revenues generated from the fees may be used only to expedite the process for the review of human drug applications. The schedule of fees is shown in table 1.

[1]For example, the average approval time for NDAs for new molecular entities (NMEs) submitted to FDA in 1989 was 22 months (range: 6 months to 47 months). The number of 1989 submissions was 26; 19 were eventually approved.

Table 1: User Fee Schedule

	Fiscal year				
Fee	**1993**	**1994**	**1995**	**1996**	**1997**
Drug application					
Fee per subsection (a)(1)(A)(i) application	$100,000	$150,000	$208,000	$217,000	$233,000
Fee per subsection (a)(1)(A)(ii) application	$50,000	$75,000	$104,000	$108,000	$116,000
Fee revenue	$12,000,000	$18,000,000	$25,000,000	$26,000,000	$28,000,000
Annual establishment					
Fee per establishment	$60,000	$88,000	$126,000	$131,000	$138,000
Fee revenue	$12,000,000	$18,000,000	$25,000,000	$26,000,000	$28,000,000
Annual product					
Fee per product	$6,000	$9,000	$12,500	$13,000	$14,000
Fee revenue	$12,000,000	$18,000,000	$25,000,000	$26,000,000	$28,000,000
Total fee revenues	**$36,000,000**	**$54,000,000**	**$75,000,000**	**$78,000,000**	**$84,000,000**

Source: Prescription Drug User Fee Act of 1992, 21 U.S.C. sec. 379h (b)(1).

The user fee act mandates that FDA make annual reports to the Congress on how the agency has implemented its authority to collect user fees and on how the fees collected have been used. The act also establishes specific times within which FDA is expected to review and act on the various kinds of applications it receives. In its annual reports, FDA is required to indicate progress in attaining these timeliness goals.

Objective, Scope, and Methodology

Considering the reauthorization of the user fee act leads to many questions—including the extent to which user fees have generated more resources for FDA, whether FDA has allocated the additional resources properly, and whether the time for FDA to review and approve NDAs has been shortened. Probably the most critical question is whether the act has allowed safe and effective new drugs to become available to patients earlier than they were available prior to user fees. The objective of this study was to examine whether the act's reporting requirements mandate sufficient information to answer this question.

This report focuses on one of several different types of applications reviewed by FDA—NDAs submitted to the Center for Drug Evaluation and Research (CDER).[2] We further concentrated on the period from submission

[2]The user fee act pertains to NDAs and supplements submitted to CDER and to product license applications and establishment license applications submitted to the Center for Biologics Evaluation and Research.

of one of these NDAs to its approval or other final status—that is, the NDA review and approval process. We chose this focus because, although the user fee act pertains to events that occur prior to or subsequent to this period, it is primarily concerned with the NDA review and approval process.[3]

Our findings are drawn from four sources. We (1) reviewed the user fee act and its legislative history, (2) reviewed FDA documents pertaining to the implementation of user fees, and (3) held discussions with relevant FDA staff. In addition, we (4) conducted an in-depth study of 1 year's worth of NDA submissions in order to understand how the drug review and approval process works at FDA.[4] Details of that work are provided in appendix II.

We conducted our work in accordance with generally accepted government auditing standards.

Results in Brief

We found that the existing reporting requirements of the user fee act, if satisfied, will provide detailed information about one aspect of the drug review and approval process—the timeliness of FDA performance. However, because FDA performance is not the sole determinant of how long the process takes, these data alone will not be sufficient to evaluate how long it takes for drugs to become available to the public, and additional data are needed. In the remainder of this report, we describe this finding in more detail and make recommendations for expanding the reporting requirements of the act.

Principal Findings

Mandated Reporting Requirements

The user fee act requires that the Secretary of Health and Human Services (HHS) submit an annual report to the Congress "stating the FDA's progress in achieving the goals" of the legislation. There are three goals that relate directly to NDAs. By 1997, FDA is to

[3]For example, the act (21 U.S.C. sec. 379g(6)(A)) can be interpreted to allow the user fees collected to be used to support activities that occur during the investigational new drug (IND) phase, such as pre-NDA meetings. This phase begins when a sponsor seeks FDA permission to begin testing a new drug in humans and ends when the sponsor submits an NDA. Also, times for the review of NDA supplements are included in the act. Supplements are additions to or changes in an approved NDA.

[4]We studied all the NDAs for NMEs submitted to FDA in 1989. FDA reviewed these NDAs during 1989 to 1992. Our interviews with the sponsors of the NDAs and the FDA staff who reviewed the applications were conducted during 1992 and 1993.

1. "review and act on complete . . . NDAs for priority applications within 6 months after the submission date;"

2. "review and act on complete . . . NDAs for standard applications within 12 months after the submission date;"[5]

3. "review and act on complete applications resubmitted following the receipt of a nonapproval letter within 6 months after the resubmission date."

The focus of these goals is on what we term "FDA action time." This period begins with the submission or resubmission of an NDA that FDA judges to be complete and ends when FDA issues an "action letter." There are three kinds of action letters: approval, approvable, or not approvable. An approval letter indicates that the NDA fully meets the statutory standards for safety and effectiveness. An approvable letter indicates that the NDA provides substantial evidence of the safety and effectiveness of the drug but additional information is required or specific conditions must be met before it can be approved. A not approvable letter indicates that the NDA does not provide the substantial evidence of safety and effectiveness required for approval.

FDA controls the starting and stopping of the clock that measures FDA action time. FDA can prevent the clock from starting by finding an NDA incomplete and refusing to file it, and FDA can stop the clock by completing its review and issuing an action letter (for example, by identifying deficiencies in the NDA and issuing a not approvable letter). FDA may begin reviewing an NDA before it is officially filed, but the clock that measures FDA action time will not start until filing.[6] Similarly, FDA may continue to review an NDA before it has been officially resubmitted—for example, after a not approvable letter has been issued—but the clock will not restart until all the deficiencies that caused it to stop have been addressed. FDA action time can be measured for all NDAs, regardless of whether they are ultimately approved, and there can be more than one period of FDA action time in the life cycle of an NDA.

The existing requirements of the user fee act mandate reporting of FDA action time and thus, if satisfied, will provide detailed information about one aspect of the drug review and approval process—FDA performance—and about one aspect of FDA performance—timeliness.

[5]For both priority and standard applications, "major amendments received within 3 months of the action due date will extend the review timeframes by 3 months."

[6]If the NDA is filed, the starting date for the clock that measures FDA action time is the date when the last piece of the application was submitted.

Improvement in FDA "on time" performance is a goal of the user fee act, and thus it is appropriate to measure progress toward this goal. FDA action time provides a good gauge of FDA's on-time performance because it measures the parts of the process that FDA is most directly responsible for and has greatest control over. Because it holds FDA accountable only for the delays it can directly affect, and because it accounts for all FDA actions, not just approvals, it is an appropriate measure of the timeliness of FDA's performance.[7]

However, the time it takes for FDA to act is not the sole determinant of the time it takes for a drug to become available to the public. Therefore, simply measuring how long FDA took for each action does not allow for assessment of whether drugs really do become available earlier.

Requirement Limitations

The information mandated by the user fee act will not be sufficient for evaluating whether the act has improved the public health because there is no requirement to

- measure how long it takes for drugs to become available to patients;
- compare timeliness data from before and after the institution of user fees in order to gauge improvement;
- determine whether improved timeliness, if it occurs, has been the only effect of the user fee act—that is, whether earlier availability has been achieved through the approval of fewer or different kinds of drugs than before.

Measurement of Time

The data for evaluating whether safe and effective drugs are reaching patients sooner are insufficient because of the difference between FDA action time (the measurement required by the act) and a measure we refer to as "time to market." Before showing this difference, however, we begin by describing the measure that has been traditionally used to evaluate FDA timeliness—"approval time."

[7]A large part of FDA's time is spent on NDAs that may never be approved. Twenty-four percent (34 out of 141) of the NDAs for NMEs submitted during the 5-year period from 1986 through 1990 had some apparently final outcome other than approval (refusal to file, not approvable, withdrawal). The range is from 10 percent (3 out of 31) in 1988 to 37 percent (11 out of 30) in 1986. We say "apparently final" because there is always the possibility that an NDA that FDA refused to file or found not approvable or that a sponsor withdrew may be resubmitted and approved in the future.

"Approval time" is the period from the receipt of a filed NDA to the issuance of the approval letter.[8] It is a combination of the time it takes FDA to identify deficiencies in a complete NDA and how long it takes the sponsor to remedy them. Approval time is not a valid measure of FDA performance because it applies only to NDAs that are approved and because it holds FDA accountable for periods of time that are controlled by the sponsor (such as the time to respond to deficiencies identified in a not approvable letter). However, as a measure of how long it takes for drugs to be made available to the public, approval time is a more valid measure than FDA action time, because it captures more of the total NDA review and approval process (which may encompass more than one period of FDA action time and also includes some of the time the sponsor takes to respond).

But the most valid measure of the three for the purpose of determining whether new drugs are reaching the public earlier is "time to market" because it encompasses all the time spent by both sponsors and FDA in getting a new drug through the review and approval process. This measure describes the period from when the sponsor of a new drug first seeks permission to market it to when FDA grants that permission.[9] Because sponsors can submit NDAs at any time and FDA can refuse to file NDAs that it judges to be incomplete, the clock measuring time to market may start before the clock measuring FDA action time or NDA approval time. Similarly, because FDA and the sponsor may not reach agreement on the final printed labeling (FPL) until after the approval letter has been issued, the clock measuring time to market may stop after the clock measuring FDA action time or NDA approval time.[10] (As a measure of FDA performance, time to market is even less appropriate than NDA approval time because it includes time spent by sponsors to put incomplete NDAs in proper reviewing order, to respond to deficiencies FDA has identified, and to dispute FDA's version of the FPL.)

[8]If the NDA is filed, the starting date for the clock that measures approval time is the date when the last piece of the application was received—that is, the date the application was considered "complete."

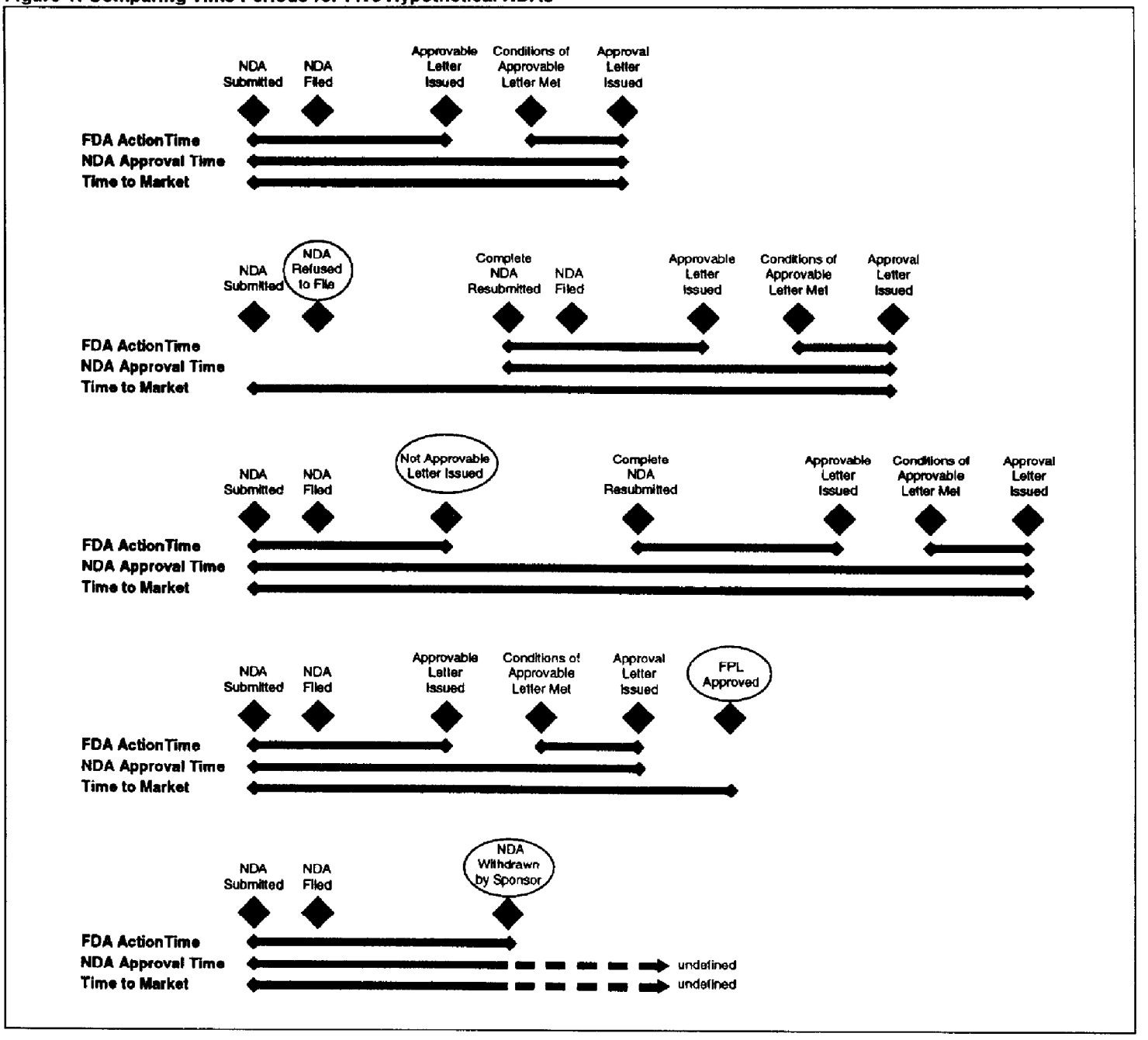
[9]The total time to market is the period from when someone first gets an idea to pursue a new drug to the time the new drug is actually available from the pharmacy. The user fee act is directed at a much shorter span of time from when the sponsor of a new drug first seeks permission to market it to when FDA grants permission to market it. We refer to this period as "time to market." It is logical to expect that what precedes this period—for example, which drugs sponsors choose to pursue and how they choose to pursue them—will affect the total time to market. Similarly, what happens after this period—for example, in the manufacturing and distribution of the drug—can be expected to affect total time to market. But both are outside the scope of the user fee legislation and therefore of this report.

[10]FDA can approve an NDA with FPL that the sponsor has not agreed to. The sponsor can dispute the FPL that FDA has stipulated in the approval letter but cannot market the drug with a label that varies from the one FDA has approved.

Figure 1 illustrates some of the major events that can occur in the life cycle of an NDA and how they can result in differences in FDA action time, NDA approval time, and time to market. It shows how the three measures of time compare for any one NDA with a given life cycle. It also shows how any one time period, for example time to market, compares across NDAs with different life cycles. The points in the figure represent events in the life cycle of an NDA that can affect the length of the three time periods. The events that differ among the five NDAs are circled. The solid horizontal lines drawn below the points represent the length of time that the various clocks are "running."[11]

[11]The scale is 0.23 inches = 1 month. Assumptions underlying the figure are that a sponsor's NDA submission date is simultaneous with FDA's receipt date; FDA makes filing decisions in 2 months; FDA issues approvable letters and not approvable letters in 6 months after the review clock starts or restarts; FDA issues approval letters 3 months after the review clock is restarted, when the sponsor has addressed all the issues raised in the approvable letter; sponsors respond to refusal-to-file actions and not approvable letters in 6 months and to approvable letters in 3 months; the approval letter is issued simultaneously with agreement on the FPL unless otherwise noted; a sponsor's withdrawal of an NDA and FDA's acknowledgment are simultaneous.

Figure 1: Comparing Time Periods for Five Hypothetical NDAs



Making Before-And-After Comparisons

The user fee act does not require the reporting of NDA approval time, the measure of FDA performance emphasized prior to the act. Instead, it requires reporting of FDA action time and establishes 1993 as the baseline for evaluating improvements.[12] There is no requirement to report on FDA action time, or any other measure of timeliness, for the years prior to the act. Thus, the existing reporting requirements do not mandate sufficient information to allow for evaluation of how the drug review and approval process under the act compares with what it was prior to user fees. Without baseline data, it will not be possible to say whether user fees have made any difference in making new drugs available more promptly.

Effects Other Than Timeliness

The user fee act seeks to increase the public health benefits of the drug review and approval process by bringing safe and effective new drugs to patients more quickly. Correspondingly, the reporting requirements of the act (and the focus of our report to this point) relate to measures of time.

However, in order to place the data on timeliness in the appropriate context, it is necessary to also have data on what is "produced" by the drug review process. That is, information about the number of new drugs, the number and breadth of indications for drugs, and the proportion of therapeutically important drugs reaching the market, as well as the rate at which unsafe or ineffective drugs are reaching the market, would tell us whether changes in timeliness were accompanied by changes in productivity. Only by having data on these items would it be possible to determine whether the drugs approved under the new system are similar, in number and general benefit, to those approved under the old system. The reporting requirements of the user fee act do not include any provisions for information about the outcomes of the drug review and approval process to be assembled.

Recommendations

Because the user fee act does not require reporting of how long the drug review and approval process is taking in total (time to market), what the outcomes from the process are (numbers and kinds of drugs), or comparable data from before and after the enactment of the legislation, it will not be possible to evaluate whether the act has made drugs available sooner. In light of this, we recommend that the Congress amend the act to

[12]It could be argued that, because it will take at least a year for user fees to be fully implemented, 1993 statistics qualify as "before" data for FDA action time. However, even if user fees had no effect on the 1993 submissions, more than 1 year's worth of "before" data is desirable. But, further, we expect that there will be some effects of the legislation evident in the 1993 data because, even though the user fee act may not be fully implemented for some time, some aspects of the act went into effect immediately. For example, FDA intended to enforce its refusal-to-file policy more strictly and sponsors were required to pay application fees, both beginning in 1993.

require the Secretary of HHS to provide the following additional information to the Congress. FDA already collects much of these data, and some of them are reported through other mechanisms.[13]

To Allow for Evaluation of the Timeliness of the Process

The Congress should require HHS to report on

- the length of the investigational new drug phase for all NDAs.
- FDA action time, NDA approval time, and time to market for all NDAs.

FDA has already defined the measurement of FDA action time and NDA approval time. FDA should measure time to market as follows. (1) Establish the date when the sponsor first submitted an NDA—the submission date, regardless of whether the NDA was deemed "complete" or filed by FDA.[14] (2) Establish the date when the FPL was approved and the sponsor had permission to market the drug—the permission date, regardless of when the approval letter was issued.[15] (3) Subtract the submission date from the permission date to obtain the time to market.

To Allow for Evaluation of the Outcomes From the Process

The Congress should require HHS to report the number of

- NDAs submitted per year and the numbers of these that were refused to file, withdrawn, found not approvable, resubmitted, or approved;
- priority and standard drugs submitted and approved;
- major and minor amendments, the number of NDA supplements for new or expanded indications, and the number of postmarketing requirements per NDA;
- and severity of postapproval problems and the rate of withdrawal of unsafe or ineffective drugs from the market.

To Allow for Before-and-After Comparisons

The Congress should require HHS to provide the recommended data for all NDAs submitted to FDA during the years prior to 1993 and all NDAs submitted during 1993 and onward. We suggest reporting the "before" data

[13]For example, the annual Statistical Report published by the Offices of Drug Evaluation in CDER.

[14]Because a sponsor's perception of when an NDA is suitable for submission and FDA's opinion of when an NDA is suitable for filing can differ, the filing date can be later than the date of first submission.

[15]Because disputes over the FPL can be contentious, the date of approval of the FPL can be later than the date the approval letter is issued.

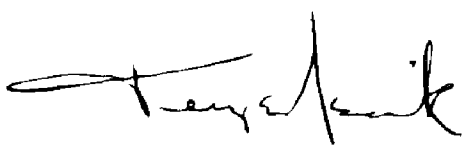
beginning at some point after the last major revision of the NDA regulations in 1985.

Agency Comments and Our Response

We provided a draft of this report to HHS. The complete text of HHS's comments and our response can be found in appendix III. HHS's comments are extensive and reflect a fundamental disagreement over the best way to evaluate the effect of user fees. Most of the differences between us derive from this disagreement. HHS sees faster FDA review times as the singular objective of the user fee legislation that merits evaluation. Although we agree that FDA review times should be monitored, we conclude that it would be beneficial to evaluate the broader effect of the legislation. The act supports our view that the Congress was interested in the effect of user fees from a broader perspective than that adopted by HHS.

Unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its date of issue. We will then send copies to the Secretary of HHS. We will also make copies available to others who are interested. If you have any questions or would like additional information, please call me at (202) 512-2900 or Robert L. York, Director of Program Evaluation in Human Services Areas, at (202) 512-5885. Other major contributors are listed in appendix IV.

Sincerely yours,



Terry E. Hedrick
Assistant Comptroller General

Contents

Abbreviations

CDER	Center for Drug Evaluation and Research
ELA	Establishment license application
FDA	Food and Drug Administration
FPL	Final printed labeling
GAO	General Accounting Office
HHS	Health and Human Services
IND	Investigational new drug
NDA	New drug application
NME	New molecular entity
ODE	Office of Drug Evaluation
P	Priority
PLA	Product license application
S	Standard

The Review and Approval Process for New Drugs

The purpose of this appendix is to familiarize the reader with the outlines of the drug review and approval process for new drugs and to define the terms used in the body of this report. The user fee act is focused on the period from submission of a new drug application to its approval or other final status. Thus, this report and the description of the process provided in this appendix also focus on that period. However, certain events outside this period have considerable effect on what happens within it and, therefore, these are reflected, at least minimally, in our description. We describe events and define terms in roughly chronological order—that is, the order in which one would encounter them if attempting to bring a new drug to market.

New Molecular Entity

FDA is responsible for many different kinds of drugs and devices. In this report, we are concerned with one category of drugs: new prescription drugs intended for humans. Within this category, we focus specifically on one particular type of new drug, the new molecular entity. FDA defines NME as an entity in which "the active moiety has not previously been approved or marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product."[1]

Center for Drug Evaluation and Research

Within FDA, CDER is primarily responsible for NMEs. The review of NMEs is divided among ten reviewing divisions, which are grouped into two offices—the Office of Drug Evaluation I (ODE I) and the Office of Drug Evaluation II (ODE II). The divisions of Cardio-Renal Drug Products, Neuropharmacological Drug Products, Oncology and Pulmonary Drug Products, Gastrointestinal and Coagulation Drug Products, and Medical Imaging, Surgical, and Dental Products constitute ODE I. The divisions of Metabolism and Endocrine Drug Products, Anti-Infective Drug Products,

[1]Moiety = part or component—in this case, of a molecule. FDA classifies new drug products into seven different types: Type 1, new molecular entity: the active moiety has not previously been approved or marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product. Type 2, new ester, salt, or other noncovalent derivative: the active moiety has previously been approved or marketed in the United States by the same or another manufacturer but the particular ester, salt, clathrate, or other noncovalent derivative is not yet approved or marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product. Type 3, new formulation: the compound is approved or marketed in the United States by the same or another manufacturer, but the particular dosage form or formulation is not. Type 4, new combination: contains two or more active moieties that have not previously been approved or marketed together in a drug product by any manufacturer in the United States. Type 5, new manufacturer: the product duplicates a drug product (the same active moiety, same salt, same formulation, or same combination) already approved or marketed in the United States by another firm. Type 6, new indication: the product duplicates a drug product already approved or marketed in the United States by the same or another firm except that it provides for a new indication. Type 7, already marketed product without an approved NDA: the NDA is the first for a drug product containing one or more drugs marketed at the time of application or in the past without an approved NDA.

Anti-Viral Drug Products, Topical Drug Products, and the Pilot Drug Division constitute ODE II. The Pilot Drug Division is responsible for anti-inflammatory, anesthetic, and analgesic drug products.[2]

Preclinical Testing

In the development of a new drug, much happens before FDA is ever directly involved. Companies search for promising chemical entities, test them in their laboratories, and conduct animal studies using them, generally without FDA's direct involvement and often without FDA's knowledge. This is the "preclinical" stage of drug development. Although FDA is generally not directly involved, if any of the studies conducted at this stage of development will be used to support a new drug application, they must ultimately meet FDA's standards. Thus, FDA may have indirect influence.

Investigational New Drug Application

FDA must be directly involved before any testing on human subjects can begin in the United States. Such tests are called "clinical trials." To get permission to begin clinical trials, a company must sponsor an IND, which summarizes the data that have been collected on the potential new drug and outlines the plans for the clinical trials.

FDA does not approve INDs. Rather, an IND goes into effect and clinical trials can begin 30 days after FDA receives the IND. The IND may go into effect sooner, if FDA so notifies the sponsor, or later, if FDA determines that it is necessary to hold the IND up for some reason. FDA can put a clinical hold on an IND during the initial 30-day period or at any other time if it believes that the application is deficient.

Clinical Testing

The IND describes the protocols for the clinical trials the sponsor plans to conduct. The purpose of these clinical trials is to determine whether a new chemical entity is safe and effective. Clinical testing is commonly divided into four phases. Phase I trials are usually conducted with a few healthy volunteers and are primarily concerned with safety. Phase II trials are also generally small but are conducted with patients and are concerned with the effectiveness as well as the safety of the drug. Phase III trials are full-scale evaluations of the drug in larger numbers of patients and are intended to conclusively demonstrate the drug's safety and efficacy. Phase IV refers to postmarketing studies, which are efforts to learn more about

[2]The Pilot Drug Division was instituted in 1989 to develop innovative ways of expediting the drug review process. At that time, it reported directly to the director of CDER. In addition to the drugs it has primary responsibility for reviewing, it handles drug abuse issues for CDER.

the drug's safety and efficacy once it has been made available to a wider population and under less tightly controlled conditions of use than is typical of clinical trials.

FDA encourages sponsors to meet with them after phase I and II trials have been completed and before embarking on a program of phase III trials. These are referred to as end-of-phase II meetings, and their purpose is to determine the safety of proceeding to phase III, to evaluate the overall plan for phase III and the specific protocols for the proposed studies, and to identify additional information necessary to support claims that will be made in the application for approval of the drug.

New Drug Application

Sponsors must obtain FDA's permission before they can market a new drug. The application for marketing approval is called a new drug application. The NDA summarizes all the evidence the sponsor has that its new drug is safe and effective for its intended uses, documents all the procedures for manufacturing the drug, and proposes labeling for the drug. In contrast to the IND, which is implicitly approved, FDA must explicitly approve an NDA before the new drug can legally be marketed in the United States.

FDA encourages sponsors to meet with them again near the end of phase III and before submitting an NDA. These are called pre-NDA meetings, and their purpose is to acquaint FDA reviewers with the NDA and to help the sponsor identify and anticipate problems that might arise in its review.

Guidelines

FDA publishes a series of guidelines for the design, conduct, analysis, and presentation of the various kinds of studies required to support INDs and NDAs. These are intended to help sponsors comply with the regulations governing new drug development and approval. FDA intends these to serve only as guidelines; they are not mandatory requirements.

NDA Contents

An NDA can consist of hundreds of volumes of information and is typically divided into several discrete but interdependent sections. These include an overall summary; a clinical data section; a nonclinical pharmacology-toxicology section; a chemistry, manufacturing, and controls section; a human pharmacokinetics and bioavailability section; a statistical section; and a microbiology section (anti-infectives only). In addition, the NDA contains report forms for the individual patients studied ("case report forms") and tabulations of the data on those forms, samples

of the drug product and validation of the methods used to produce it, and proposed labeling for the drug.

NDA Review Teams

The members of the teams that review the NDA correspond to the sections of the NDA. They include reviewers from the particular division to which the NDA has been assigned as well as consultants from other divisions as needed. The primary members of the review team can include medical reviewers, pharmacologists, chemists, microbiologists, biopharmaceutical consultants, biostatistical consultants, and consumer safety officers. Ultimately, the team can include the supervisors of each of the primary reviewers, the director of the division, the director of the office, and, rarely, the director of CDER.

Refusal to File

Once the NDA is received, FDA has 60 days to determine whether it will be officially filed. If FDA finds that the NDA is sufficiently complete to permit a substantive review, it can file and continue to review it. If FDA finds that the NDA is not sufficiently complete to permit a substantive review, the agency can "refuse to file" the application. If FDA refuses the NDA, review of the NDA may not continue and the review clock stops. Sponsors have the option of meeting with FDA to discuss the agency's grounds for refusing to file the NDA and can insist that the NDA be filed "over protest."

Classification System

When an NDA is received, and sometimes during the IND process, FDA tentatively classifies the new drug according to its therapeutic potential. Final classification is performed when the NDA is approved. Prior to 1992, NDAs were primarily classified according to three types:

"Type A, important therapeutic gain: the drug may provide effective therapy or diagnosis, by virtue of greatly increased effectiveness or safety, for a disease not adequately treated or diagnosed by any marketed drug. Or the drug may provide improved treatment of a disease through improved effectiveness or safety, including decreased abuse potential."

"Type B, modest therapeutic gain: the drug has a modest, but real, potential advantage over other available marketed drugs. Examples include greater patient convenience, elimination of an annoying but not dangerous adverse reaction, potential for large cost reduction, less frequent dosage schedule, or useful in a specific subpopulation of those with disease (for example, those allergic to other available drugs)."

"Type C, little or no therapeutic gain: the drug essentially duplicates in medical importance and therapeutic usage one or more already marketed drugs, offering little or no therapeutic gain over existing therapies."

Currently, FDA classifies NDAs as eligible for priority (P) or standard (S) review. Most NDAs that formerly would have been classified type A or B are now classified P, and those that were formerly classified type C are now classified S. These classifications are mutually exclusive.

An NDA may also have a number of other designations, including "AA," "orphan," "for expedited review," and, most recently, "for accelerated approval." These designations are in addition to the new drug's classification as P or S and are not mutually exclusive. For example, if appropriate, a new drug could be designated as both an "orphan" and "for expedited review."

In 1987, in response to the AIDS crisis, FDA instituted a new classification—type AA, for any drug product being developed for the treatment of AIDS or HIV-related disease. An AA classification signifies that the drug has top priority.

A sponsor may request orphan designation for its new drug if the drug is for the treatment of a rare disease or condition—that is, one that affects fewer than 200,000 persons in the United States. It can also be one that affects more than 200,000 persons in the United States if there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from sales of the drug in the United States. Orphan designation offers numerous benefits to the sponsor including exclusive licenses, research grants, and tax credits. Orphan designation was made possible by the 1983 Orphan Drug Act (Public Law 97-414), whose primary purpose was to bring about the development of drugs that are needed but not commercially attractive because they address very small markets.

A sponsor can also request that its new drug be considered eligible for review under the procedures outlined in the 1988 subpart E interim rule (21 C.F.R. 312 subpart E). "Subpart E" drugs are intended to treat life-threatening and severely debilitating illnesses. Such drugs benefit from a number of efforts intended to expedite their approval, including high priority for FDA's IND and NDA reviewing resources.

In 1992, FDA issued new regulations allowing accelerated approval of certain new drugs for serious or life-threatening illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment. Under these regulations, FDA will consider basing approval on evidence of the drug's effectiveness on "surrogate endpoints" or modifying or restricting distribution and use of the new drug if safety considerations warrant.[3] In addition to providing for accelerated approval, the regulations allow for expedited withdrawal from the market if necessary.

Review Clock

Previously, FDA had a maximum of 180 days from the receipt of an NDA to review and take a "final action" on the application.[4] Final actions included refusing to file the NDA, acknowledging an applicant's withdrawal of the NDA, or issuing an action letter. This 180-day period was called the "review clock."

Currently, under the user fee act, the "review clock" starts only with the receipt of an NDA that is accepted for filing and stops when FDA acknowledges a withdrawal or issues an action letter. FDA refusal to file an NDA therefore occurs "off the clock." The user fee performance goals distinguish between P and S drugs, allowing FDA 6 months to issue an action letter for P drugs and 12 months for S drugs.

The due date can be extended by mutual agreement of the sponsor and FDA or by amendments to the NDA. Amendments are submissions of additional information to an unapproved NDA and contrast with supplements, which are additions to or changes in an approved NDA.[5] Amendments can be classified as major or minor, depending on how much new information they contain.

[3]A surrogate endpoint is not the endpoint of primary interest but one that is believed to be a good indicator of it. For example, with cancer, the endpoint of primary interest is whether the patient lives or dies. Surrogate endpoints include whether the tumor shrinks and even whether the rate of growth of the tumor is slowed.

[4]The date of submission is the date the sponsor puts on the cover sheet for the NDA, and the date of receipt is the date when FDA's document center stamps the NDA as having being received. In practice, there is generally little difference between these two dates. Throughout this report, we use the term "submission" to refer to the sponsor's date and the term "receipt" to refer to FDA's date.

[5]Submissions of additional information to an unapproved supplement are called supplemental amendments.

Previously, major amendments could extend the review period for a maximum of 180 days.[6] Extensions for amendments to different disciplines (for example, chemistry versus pharmacology) ran concurrently, but amendments to the same discipline were additive. FDA extended the review period for the amount of time necessary to review the additional information and had guidelines for how large an extension was warranted for each different kind of amendment.

Under the user fee program, only major amendments can extend the due date, and according to FDA, only one extension for a maximum of 3 months is allowed.

In the course of its review, FDA may need additional information about or may note easily correctable deficiencies in the NDA. If so, it may send "information request letters" or "interim deficiency letters" to the sponsor. Responses from the sponsor, depending on how much information they contain and how long the FDA reviewers anticipate they will need to review the information, can be classified as correspondence or as amendments. Information request letters, interim deficiency letters, and correspondence have no implications for the review clock, but some amendments, as noted above, can extend it.

Withdrawals

The sponsor of an NDA may withdraw its NDA at any point in the review process, even before FDA makes a filing decision. Such withdrawals are made "without prejudice to refiling" and do not preclude future resubmission of the NDA. FDA can also withdraw an NDA from active consideration if the sponsor does not respond to an approvable or not approvable letter in a timely fashion. FDA's letter acknowledging the sponsor's withdrawal stops the review clock.

Action Letters

After reviewing the NDA and reaching a decision about its approvability, FDA can issue one of three action letters. The issuance of any of these three letters stops the review clock.

1. FDA can issue an "approval letter" after it has determined that the NDA "has fully met the statutory standards for safety and effectiveness, manufacturing and controls, and labeling." The date of this letter is the

[6]Prior, that is, to the institution of user fees. According to the user fee legislation, "major amendments received within 3 months of the action due date will extend the review timeframes by 3 months."

date of approval of the NDA, and marketing of the drug is permitted from this date.

2. FDA can issue an "approvable letter" when it has determined that the NDA has provided substantial evidence of the safety and effectiveness of the drug but "additional information must be submitted or specific conditions must be agreed to by the applicant" before the NDA can be approved.

3. FDA can issue a "not approvable letter" if it determines that the NDA "does not provide the substantial evidence of safety and effectiveness required."

Advisory Committees

FDA has established a number of advisory committees to assist in the evaluation of NDAs. Their purposes are to "(1) provide outside expert advice on scientific and medical issues related to new drug approvals, (2) resolve disputes between industry and the review team regarding scientific requirements, (3) generate increased acceptance for agency policy decisions, and (4) speed up the process of new drug review." The committees' recommendations are not binding on the agency.

Postapproval

FDA's concern about and regulatory control over a new drug does not end with its approval. FDA may have required phase IV studies of the sponsor; if so, FDA continues to monitor and evaluate these studies. Whether or not the sponsors have agreed to phase IV studies, all sponsors must meet postapproval reporting requirements. These include "15-day alert reports," "periodic safety reports," "field alert reports," annual reports, and findings from any phase IV studies they may have voluntarily undertaken. Also, sponsors often continue to explore different uses for their drugs and submit supplements to the NDA.

FDA may withdraw its approval of an application at any time. Approval may be withdrawn for a number of reasons, including new evidence that the drug is not in fact safe and effective when used under the conditions approved in the NDA or failure to meet postmarketing reporting requirements.

Statistical Reports

CDER publishes annual statistical reports that provide information on, among other things, the NDAs for NMEs submitted that year. It also provides information on NDA approvals and how long they took. FDA publishes two statistics on approval time: total approval time and FDA approval time.

Total approval time is the total time from the date of FDA's receipt of the NDA to the date FDA issues an approval letter. FDA approval time is total approval time minus the time required by the sponsor to respond to an approvable or not approvable letter or to resubmit the application after a refusal to file or withdrawal by the sponsor.

Figure I.1 illustrates the timelines for drug development, clinical trials, and FDA drug approval and how they relate to one another, and it also shows the portion of the three timelines covered by our study. Figure I.2 illustrates the steps in the NDA review and approval process.

Figure I.1: Four Timelines Compared

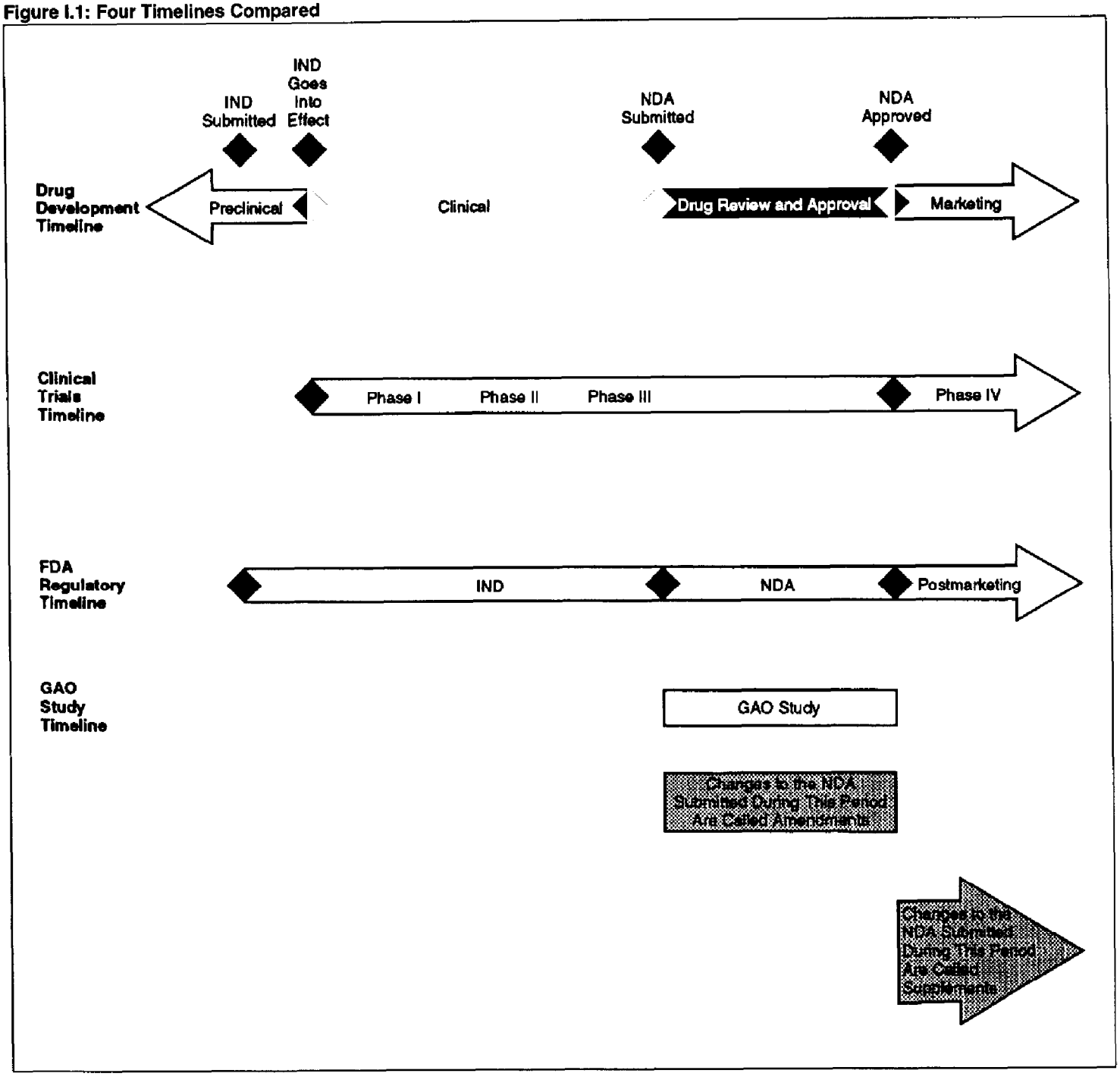
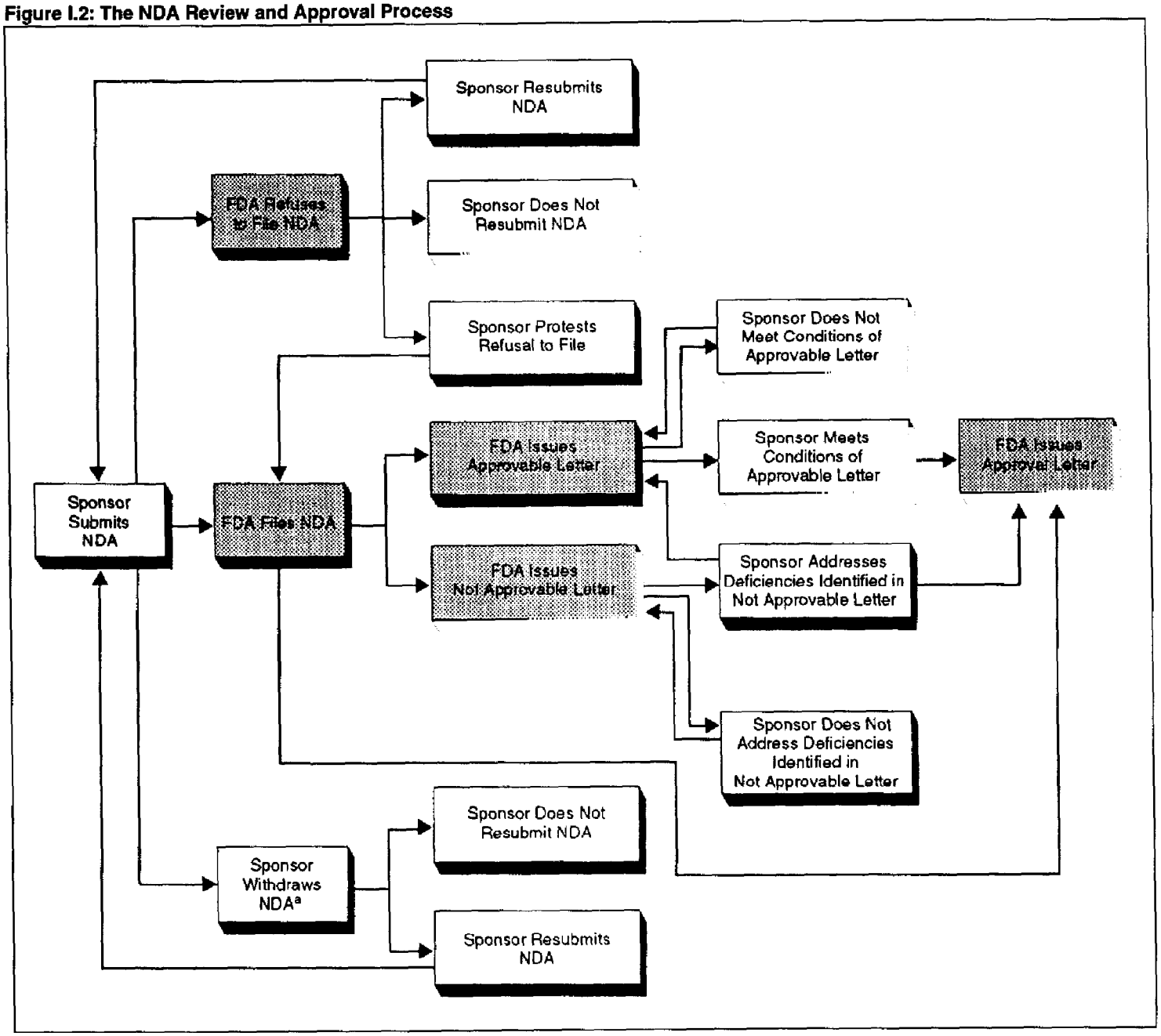


Figure I.2: The NDA Review and Approval Process



[a]Sponsor can withdraw NDA at any point in the process.

A Description of GAO'S Review of 1989 NDA Submissions

Objective

The objective of this review was to understand the factors that drive FDA's drug review and approval process and that influence how long it takes.

Scope

FDA receives many different types of NDAs. We focused on one type, NDAs for NMEs, because we judged it to be the most controversial and to use the most resources. We examined all the NDAs for NMEs submitted to FDA in 1989 and reviewed by FDA during 1989-92. We selected this sample in order to have a sample as recent as possible while still allowing for enough time to have passed so that most of the NDAs would have matured (that is, would have been approved or found not approvable). This sample also had the advantage of being several years after the last major overhaul of NDA regulations, the "1985 NDA Rewrite."

We chose to examine all 1989 submissions, not just approvals as is typically done, because we wanted to see a fuller range of NDA review experiences. We believed that this was important because over one quarter of the NDAs submitted in 1989 did not result in approval (and, based on what the sponsors told us, many of these are likely never to result in approval).

Our sample captures much of the variety that exists in the types of NDAs for NMEs that can be filed and the kinds of issues that can arise in review and approval. The indications for which the drugs are proposed range from dermatoses to insomnia to cancer. The medications include capsules and ointments and injections. Sponsors represented in the sample of applications include large and small companies, new and established companies, companies experienced with assembling NDAs, as well as those for whom this was the first NDA. The applications include examples of NDAs that FDA refused to file, found not approvable, or approved, as well as NDAs that the sponsor chose to withdraw. Finally, drugs representing most of FDA's various classifications (for example, therapeutic importance) and designations (for example, orphan drug) are included in the sample.

Some features of the 1989 NDAs we examined are described in tables II.1 and II.2.

Table II.1: Features of the 1989 NDA Submissions[a]

Feature	Number	Percent[b]
Status as of August 1993		
Refusal to file	1	4
Withdrawn by sponsor	4	15
Not approvable	2	8
Approved	19[c]	73
Therapeutic classification[d]		
A	5	19
B	6	23
C	15	58
Other classifications[e]		
AA	1	4
Orphan	4	15
Subpart E	5	19
Reviewing division		
Office of Drug Evaluation I		
Cardio-renal drug products	3	12
Neuropharmacological drug products	3	12
Oncology and pulmonary drug products	3	12
Medical imaging, surgical, and dental products	3	12
Gastrointestinal and coagulation drug products	4	15
Office of Drug Evaluation II		
Metabolism and endocrine drug products	3	12
Anti-infective drug products	5	19
Antiviral drug products	1	4
Pilot Drug Division		
Anti-inflammatory, anesthetic, and analgesic drug products	1	4

[a]Number = 26. Only new drugs that were classified as NMEs when they were received and when they were approved (or, if they were not approved, as of August 1993) are included in our sample. If an NDA was classified as an NME when it was received, but was subsequently reclassified because of the approval of another drug, or, if an NDA was originally classified as something other than an NME but was reclassified as an NME when it was approved before another drug that had been classified as an NME, it is not included in our sample.

[b]Percentages do not always total 100 because of rounding.

[c]One of the approved drugs was subsequently withdrawn from the market because of safety problems.

[d]The therapeutic classification of one drug changed during the course of the review. It was initially classified C but was reclassified to A. We chose the A classification because it was in effect at the time of approval.

[e]Percentages for AA, orphan, and subpart E drugs do not total 100 because a drug may or may not have one or more of these classifications.

Table II.2: Features of the Approved 1989 Submissions[a]

Feature	Mean	Range
Approval times (in months)[b]		
A	11	6-17
B	20	15-24
C	29	14-47
AA	11	11-11
Orphan	17	13-22
Subpart E	19	11-24
Overall	22	6-47
Number of amendments filed per application		
Major	5	0-10
Minor	18	4-41

[a]Number = 19.

[b]Total approval time—that is, from FDA's date of receipt to FDA's date of approval of the NDA. No differences were found when the sponsor's date of submission was used instead of FDA's date of receipt. Rounded to the nearest whole month.

For each case, our focus was on the information generated solely during the NDA phase—that is, from submission of the NDA to approval or another final outcome. However, we explored the pre-NDA and postapproval phases to the extent made necessary by issues arising during the NDA phase.

Methodology

For each of the 26 NDAs in our sample, we reviewed FDA's file, which contains the original application, additions and amendments to the application, correspondence between FDA and the sponsor pertaining to the application, and FDA's reviews of the application's contents.[1] The purpose of this review was to allow us to create a list of the factors that apparently influenced how and when decisions were made as the applications moved through the process.

Once we had established our independent sense of the significant factors in each case, we discussed the application and its review with any staff members at FDA who took some part in reviewing the application. The protocol for this discussion included an opening statement from our staff

[1]Four of the drugs in our sample were submitted in two different forms—for example, cream and ointment. FDA counts these as two separate NDAs and identifies one as the new molecular entity (type 1) and the other as a new formulation (type 3), although they may be reviewed simultaneously. We counted these pairs as only one NDA and reviewed both, focusing on whichever one FDA had designated as the NME.

indicating our desire to understand all the factors that influenced the review of the specific NDA. Of particular interest were any characteristics of the NDA or the review that presented challenges for either FDA or the sponsor. Once our introductory statement was concluded, FDA staff were asked to identify the factors they thought were most significant. In instances in which FDA staff preferred to be prompted, we went through the list of issues we had identified by our own review of the files.

The protocol for our interviews with the sponsors was similar to that employed with FDA staff. Pharmaceutical firms were encouraged to have present individuals who could speak to all facets of the NDA review.[2] The meetings began with our introductory statement, similar to that made at FDA sessions. The sponsor's representatives could then either list the factors that they saw as having influenced the review and approval process or respond to our prompts. However, when the former option was selected, we did ask for comments on any issues we had encountered in our independent review of the NDA files that had not been raised by the sponsor's staff. (The same was true in our discussions with FDA in which the agency's staff failed to mention an issue that had surfaced through our review.)

Finally, in both sets of discussions, our interest went beyond a simple listing of the issues raised by FDA, the sponsor, or our own review of the NDA files. For each issue we also determined its "generalizability." That is, our interest was in determining the extent to which the issue was idiosyncratic to the specific NDA, characteristic of all NDAs, or somewhere between these two extremes (for example, characteristic of this class of drugs and of applications relying on foreign data but not of all NDAs).[3]

[2]We were unable to discuss the NDA with the sponsor in one case because the person whom the sponsor thought was most appropriate for us to talk with was no longer at the company.

[3]We reviewed NDA files and conducted interviews with FDA and sponsors from June 1992 to May 1993.

Comments From Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Office of Inspector General

Washington, D.C. 20201

MAY 9 1994

Ms. Eleanor Chelimsky
Assistant Comptroller General
United States General
Accounting Office
Washington, D.C. 20548

Dear Ms. Chelimsky:

Enclosed are the Department's comments on your draft report, "FDA User Fees: Current Measures Not Sufficient for Evaluating the Legislation's Impact on the Public Health." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

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

Sincerely yours,

June Gibbs Brown
Inspector General

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
COMMENTS ON THE GENERAL ACCOUNTING OFFICE DRAFT REPORT
"FDA USER FEES: CURRENT MEASURES NOT SUFFICIENT FOR EVALUATING THE LEGISLATION'S IMPACT ON THE PUBLIC HEALTH"

GENERAL COMMENTS

See comment 1.

Contrary to the implication of the report's title, the Prescription Drug User Fees Act of 1992 (Act) does not require that the Department's Food and Drug Administration (FDA) be able to evaluate the direct impact of user fees on public health. Evaluation of "improvement in the public health" requires a complex multi-factorial analysis that goes much beyond the Act provisions and the General Accounting Office (GAO) recommendations.

See general comments.

Rather, the primary purpose of the Act is to provide FDA with the resources needed to review applications within specified time frames while also providing drug sponsors a way of accurately predicting when product reviews will be completed. The reports required by the Act focus on the setting and meeting of recruitment and performance goals. It is hoped that by making available additional resources to expedite the review of human drug applications, the public health also will be improved. Thus, in evaluating the success of the program, the emphasis is properly focused on whether FDA was actually successful in speeding its reviews of these products, not on a specific improvement in the public health.

The terms of the Act were carefully developed with the input of the prescription drug industry, FDA, and the Congress to ensure that it would be fair to all parties. The report should acknowledge that FDA can only act on those applications submitted to it. Industry submissions are a reflection of industry research and development decisions and successes. External forces such as technological discoveries and health care reform have greater influence on types of drugs approved than does FDA's user fee performance.

In addition to the differences in interpretation on the Act's goals, we have the following comments.

1. The report determined that the Act's reporting requirements are incomplete as a measure of approval performance. This is fully acknowledged by FDA, by industry and by the drafters of the legislation. The specific measures referenced in the statute were negotiated between the FDA and the industry to measure progress toward meeting the performance goals funded by the user fees paid by the industry. These goals reflect more predictable performance by FDA reviewers than had been possible under the previous procedures. The FDA, industry, and the Congress all agreed that such improvements in performance would lead to shorter

See comment 2.

approval times. Other performance measures and tracking systems also are in place to supplement these specific measures. They were established in response to the Act, the Government Performance and Results Act (GPRA), the FDA strategic plan, and ongoing management interest. They are refined and updated as changes are made to the review program.

2. The report, by focusing on new molecular entities specifically for new drugs, does not present an entirely accurate description of both the intent of the Act and the complexity of its implementation. It is important to note that the Act applies to other New Drug Applications (NDA), Product License Applications (PLA), Establishment License Applications (ELA), and certain supplemental NDAs, PLAs, and ELAs.

See comment 3.

3. The report suggests that FDA determine whether improved timeliness in reviewing NDAs comes at the cost of approving fewer drugs or different kinds of drugs. As indicated above, the Act does not in any way change the mix or number of NDAs submitted to the agency for review. Prescription drug firms are still at liberty to submit their applications whenever they choose. They are also at liberty to develop drugs in any category they choose and for any indications. Therefore, the decisions regarding the number and kind of applications still remain in the control of the industry, not FDA. The number and kinds of applications have always varied from year to year and probably will continue to do so. The Act does provide that fees be calculated to cover the FDA cost of reviewing and it permits FDA to hire staff as necessary to accomplish the goals.

See comment 4.

Furthermore, the Act's implementation plan establishes goals for FDA review of applications which generally are not amenable to manipulation. For example, the goal of having completed the review of 90 percent of received applications within the 6 and 12 month time frames could not be accomplished by attempting to complete review of fewer applications than have been received or by reviewing the less complicated applications and ignoring the more complex ones. This misunderstanding of the review process in the report should be corrected.

See comment 5.

4. The report states that, "FDA can prevent the clock from starting by finding an NDA incomplete and refusing to file it, and FDA can stop the clock by completing its review and issuing an action letter (for example, by identifying deficiencies in the NDA and issuing a not approvable letter)." This suggests that FDA controls the clock for its own purposes rather than as a legitimate means of assessing accountability and responsibility. However, the report does

See comment 6.

not address the changes FDA has initiated in accounting for timeliness and accountability as a result of the Act.

The report should mention the reason for FDA's Refusal to File (RTF) policy which is based on the recognition that FDA can no longer afford to expend review resources on incomplete applications and allow the development of NDAs on FDA's review clock. The report also should acknowledge that this policy already has begun to produce a new accountability for quality submissions in the industry. The report also should reference the industry practice of filing NDAs for reasons other than their being complete and ready for review. The industry has a number of incentives to submit incomplete NDAs to FDA, including in-licensing agreements with other firms, end-of-year bonuses paid by companies to members of the development team for filing, trying to jump the review queue, and contractual agreements between contract research organizations and sponsors. Finally, the report should mention that the RTF decisions are reviewed by Center for Drug Evaluation and Research upper management, a representative of the Center for Biologics Evaluation and Research, and FDA's Ombudsman to ensure regulatory and scientific consistency.

See comment 7.

The report also implies that FDA can "stop the clock" by finding a deficiency and issuing a not approvable (NA) letter. The report should mention that this was a practice under the old system that has been discontinued under the Act. The user fee clock was specifically designed to end that practice by mandating that an action letter could only be issued when a complete review is finished.

See comment 6.

While the report mentions that FDA can review some material "off the review clock," it does not mention that FDA encourages sponsors to begin preparing responses to deficiencies in one discipline before the review of all disciplines is complete by sending deficiency letters prior to issuance of COMPLETE action letters. FDA recognizes that this practice allows the industry to develop responses "off the clock," but we believe it is in the best interest of fully reviewing applications as expeditiously as possible.

5. We believe that the concept of "time to market" as defined in the report is of questionable value toward accomplishing GAO's stated goal. The date the company chooses to submit an application has often been determined by factors having no bearing on the quality of the submission or the completeness of the firm's research. Under the scenario proposed by GAO, a company could decide to submit a totally inadequate "NDA" at the end of Phase II and the "time to market" clock would start at that point. This practice is one that FDA is attempting to discourage. Such premature

See comment 8.

submission does not in any way speed up the review, and may actually cause additional time to be consumed attempting to review data that are inadequate to answer questions of safety and effectiveness.

The concept of "time to market" is a valuable concept if properly defined. Time to market involves the discovery time, development time, review time, and launch time. Discovery time is totally within the domain of the sponsor. Development time is time between a sponsor's filing an Investigational New Drug exemption (IND) and the point at which the sponsor files a complete dossier that details the data necessary for review; in other words, the NDA. This time also is under the domain of the sponsor. FDA's role during the IND stage of development is to review protocols that are submitted and to review required reports of safety data from the sponsor. FDA is required to review initial protocols within 30 days of their receipt and issue a clinical hold if there is a reason to expect safety concerns in exposed individuals. FDA is not required to respond in any way if there are no safety concerns raised by the protocol. If a question of safety arises at any time during the IND stage, FDA may put a clinical hold on further human exposure to the proposed new drug until such concerns are satisfactorily resolved. The launch phase is also beyond FDA's purview in the great majority of cases. To cloud the distinction between the development stage and the review stage, by arbitrarily including the date a sponsor chooses to submit an NDA regardless of its completeness, as suggested by GAO, would set the review process back to a failed system for assigning responsibility and accountability for the various elements in the process. Such system would be particularly inappropriate when FDA is requiring all firms to pay for the review of drugs and there is a need to determine where resources need to be placed to effect improvements to the process.

See comment 9.

6. We believe that the report is incorrect in its discussion regarding final product labeling (FPL). It is not true that "...because FDA and the sponsor may not reach agreement on the final product labeling until after the approval letter has been issued, the clock measuring time to market may stop after the clock measuring FDA action time or NDA approval time." The report has misinterpreted FDA's policy of approving an application based on acceptable draft labeling in order that the sponsor not have to go to the expense of printing FPL until the wording is acceptable to both parties, or it misinterprets as standard operating procedure FDA's policy allowing it to approve, in certain circumstances, final labeling without the concurrence of the sponsor. Far from being standard operating procedure, FDA has never used this authority.

See comment 10.

See general comments.

See comment 11.

7. The report states that the Act does not provide for "before and after" comparisons. While this statement is true, this was not the intent of the Act. Of great concern to the industry were the lengthy review times, particularly for longer than "average" applications. Measures of averages do not reflect the wide variances in review performance that were and are of concern. Therefore, the Act establishes phased-in goals of achieving complete reviews within specified time frames. When the Act is fully implemented, FDA will complete at least 90 percent of all reviews within the specified time frames. Therefore, the new system is not comparable to the previous system. Furthermore, if FDA meets its goal, there will be a significant decrease in the average review times as well as the individual review times. It is measurement of FDA's progress toward meeting its goal that is significant to the Congress and to the industry.

We do not agree with the report's conclusion that it will be difficult to determine whether new drugs will be available more promptly as a result of the Act. Submission dates and approval dates are a matter of public record. Such measures will always be available, even if not calculated directly by FDA. As stated above, meeting the goals established under the Act will clearly make drugs available more promptly as a result of shorter FDA review time. Other factors are not within the control of FDA. Nor is it the intent of the Act to change the role and responsibilities of the sponsors, whose discovery times and development times are not a matter of public record.

GAO RECOMMENDATION:

We recommend that the Secretary of HHS provide to the Congress the following information, in addition to that mandated by the user fee act. Much of this data is already collected by FDA and some of it is reported through other mechanisms.

(A) To Allow for Evaluation of the Timeliness of the Process

Report the length of the IND phase for all NDAs ultimately submitted.

Report FDA action time, NDA approval time, and time to market for all NDAs submitted to FDA. FDA has already defined the measurement of FDA action time and NDA approval time. Time to market should be defined as follows:

-- Establish the date that the sponsor first submitted an NDA--the submission date, regardless of whether the NDA was deemed "complete" or filed by FDA.

-- Establish the date that the final product labeling (FPL) was agreed to and the sponsor had permission to market the drug--the permission date, regardless of when the approval letter was issued.

-- Subtract the submission date from the permission date to obtain the time to market.

(B) To Allow for Evaluation of the Outcomes from the Process

Report:

-- the number of NDAs submitted per year, and the numbers of these that were refused to file, withdrawn, found not approvable, resubmitted, or approved.

-- the number of priority and standard drugs submitted and approved.

-- the number of major and minor amendments, the number of NDA supplements for new or expanded indications, and the number of post-marketing requirements per NDA.

-- the number and severity of post-approval problems and the rate of withdrawal of unsafe or ineffective drugs from the market.

(C) To Allow for Proper "Before and After" Comparisons

Provide the recommended data on all NDAs submitted to FDA during the years prior to 1993 and all NDAs submitted during 1993 onward. We suggest reporting the "before" data beginning at some point after the last major revision of the NDA regulations in 1985.

HHS COMMENT

See comment 12.
See comment 13.

We agree with the GAO report's finding that the Act's existing reporting requirements will provide detailed information on the timeliness of FDA's performance on the drug review and approval process. However, we do not concur that the additional data recommended by GAO will help to measure FDA's timeliness in completing reviews. As we have stated above, many elements of the recommended data are not under FDA control and will not be affected by the imposition of user fees or the additional resources FDA will be using in the review process. In addition, the "time to market" reflects events having little to do with the scientific elements of the review process.

See comment 14.

The FDA already publishes several statistical reports that provide information on, among other things, total approval time and FDA approval time; however, most of the data recommended by

GAO is not specifically collected at this time. Furthermore, the recommended data would not achieve GAO's desired result to facilitate evaluation of the impact of user fees on the public health because none of the recommended data elements relates directly to public health.

This recommendation appears to commingle a number of factors unrelated to completing a product review with those that are essential. For example, the imposition of post-approval requirements is not integral to the review process. Such requirements may, in fact, help to reduce review time by providing a mechanism to resolve questions without delaying approval. It also should be noted that, given the intent of the Act and the resulting review process, calculating the numbers of post-approval requirements per NDA would have no meaning.

See comment 15.

Finally, as we have also indicated above, calculating the recommended data for submissions prior to 1993 not only would be difficult, but also the data so calculated would not be comparable to that related to post-1993 submissions. The Department is no longer operating in the same way that it was before. For example, action letters issued prior to 1993 are not comparable to current action letters because there was no requirement that they be complete. Many of the recommended calculations would encourage a return to a lack of responsibility and accountability for product availability.

See comment 16.

See comment 17.

The following are GAO's comments on the May 9, 1994, HHS letter.

GAO Comments

Most of HHS's comments reflect a basic disagreement with us over the best way to evaluate the effect of the user fee act. HHS also makes a number of specific comments about our report. We address the broader issue first and then the remaining specific comments.

General Comments

According to HHS, "the primary purpose of the Act is to provide FDA with the resources needed to review applications within specified time frames while also providing drug sponsors a way of accurately predicting when product reviews will be completed." HHS goes on to indicate that the only data FDA is required to submit are those that measure FDA performance. We agree that improvement in FDA review times is a central objective of the act, that data on FDA performance are critical for evaluating the effect of user fees on FDA review time, and that these data are the only data FDA is currently mandated to report.

However, we conclude that additional data would be beneficial in evaluating the broader effect of the legislation. The act supports our view that the Congress was interested in the effect of user fees from a broader perspective than that adopted by HHS. It states:

"Prompt approval of safe and effective new drugs is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease;

"the public health will be served by making additional funds available for the purpose of augmenting the resources of the Food and Drug Administration that are devoted to the process for review of human drug applications."

As this language indicates, the public will realize a benefit from faster FDA review if improved agency performance translates into drugs becoming available to patients more rapidly. However, from our examination of the drug review and approval process, we know that the time it takes drugs to reach the public is not simply a function of FDA review times. That is, it is possible that FDA review times can decrease without a corresponding decrease in the time to market. In this situation, if FDA did not provide data on time to market in its annual report, the Congress would be left with the impression that drugs were being made available faster when that was not true. That is why we recommend that in its annual report to the Congress

FDA provide data on how long it takes for drugs to become available in addition to data on FDA performance.

Specific Comments

1. The title of the report indicates that the effect of the legislation on the public health cannot be evaluated with the data FDA is currently mandated to provide. There is no implication that the act currently requires that FDA evaluate the effect of user fees on the public health. If that were the case, there would be no need for our recommendation.

2. The fact that all parties expect improvements in FDA performance to lead to shorter approval times does not mean that this will necessarily happen. That is why we recommend that data on approval times be reported to the Congress. In addition, given that some of these data on approval times are already collected, it would be useful to include them in the annual report to the Congress.

3. The draft we provided to HHS indicated that implementation issues were not the focus of our study. Additionally, the draft explicitly stated that the act applies to product license applications, establishment license applications, and certain supplemental NDAs, PLAs, and ELAs as well as NDAs. Our focus is specifically on whether the act mandates the data necessary for the Congress to evaluate its effect in allowing new drugs to reach the public more quickly.

4. HHS is concerned that changes that naturally occur in the mix and type of products submitted to FDA will somehow be interpreted as a result of user fees. A careful analysis of the data that we suggest be reported would avoid such an error.

5. We make no assertion that the goals for action time stated in the act will be manipulated by FDA. Rather, we demonstrate that the relationships between FDA action time, NDA approval time, and time to market are not deterministic. That is why shortening FDA action time may not lead to shorter time to market.

6.Our description of how the clock works was meant not to suggest that FDA will control the clock for its own purposes but simply to indicate that the starting and stopping of the clock is triggered by FDA actions.

7. FDA's refusal-to-file policy was not the focus of the study and is relevant largely to the extent that it can influence the different measures of time.

8. We agree that the proposed measure of time to market does not capture the entire period involved in drug development. However, it is a more valid indicator of how long it takes drugs to reach patients than what is currently required by the legislation. Essentially, time to market measures the interval between when the sponsor thinks the product is ready for marketing and when FDA has approved it.

9. The objective of our measure of time to market is not to assign "responsibility and accountability." Rather, this measure is intended to provide information on whether the time from initial submission of an NDA to the time the drug can be marketed has changed.

10. HHS disputes out analysis of the possible effects of delays in reaching final agreement on product labeling, but we are unclear on what HHS believes is incorrect. We both agree that FDA may approve an application before there is final agreement on labeling. That would appear to be a straightforward example of a case in which a measure of time to market would capture a factor that can create delays after FDA has given its formal approval of a drug. HHS agrees that it has a "policy allowing it to approve, in certain circumstances, final labeling without the concurrence of the sponsor." We never indicate that this is "standard operating procedure"; we indicate merely that it creates the possibility for discrepancy between FDA action time, FDA approval time, and time to market.

11. HHS argues that the information we call for is a matter of public record and will always be available even if not directly calculated by FDA. The availability of the information would be more certain and its analysis more complete if it were included in FDA's reporting to the Congress.

12. The additional data are not necessary to help measure FDA's timeliness in completing reviews; rather, they are necessary to measure time for activities that do not directly involve FDA but do affect how quickly drugs reach the market.

13. HHS assumes that "many elements of the recommended data . . . will not be affected by the imposition of user fees or the additional resources FDA will be using in the review process." We argue that this assumption should be verified with data. We cannot know beforehand all the effects the act will have.

14. All the information we request can be obtained from action letters (number of postmarketing requirements per NDA) or from FDA's

management information system (IND filing dates, NDA submission dates, NDA filing dates, number and severity of postapproval problems). Further, all the recommended data elements relate directly to determining when new drugs are available or to whether the act has had unintended effects on the outcomes of the review and approval process.

15. Postapproval requirements "may . . . help to reduce review time by providing a mechanism to resolve questions without delaying approval." Our concern is that, in response to time pressure, questions that were answered before approval may now be pushed to after approval.

16. All the data that we recommend be reported are available for the period prior to 1993. The interpretation of some of the data will not be straightforward and can best be accomplished by having information on all three recommended measures—FDA action time, NDA approval time, and time to market.

17. We disagree that "the recommended calculations would encourage a return to a lack of responsibility and accountability for product availability." The availability of data on both FDA review time and sponsor's time will make accountability for all parts of the process clearer.

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