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BY THE COMPTROLLER GENERAL

**Report To The Subcommittee On Science,
Research, And Technology, House
Committee On Science And Technology
OF THE UNITED STATES**

**FDA Drug Approval--A Lengthy Process
That Delays The Availability Of Important
New Drugs**

The average time required by the Food and Drug Administration to approve drugs--some of which could provide increased therapeutic benefits--is 20 months, including 17 months of FDA time and 3 months of industry time. This lengthy approval process delays the availability of the therapeutic benefits a drug may provide to the public. Some important drugs (those providing a major or modest therapeutic gain over any marketed drugs) have been approved by foreign countries in less time than in the United States.

FDA has established goals to reduce the processing time for important drugs by 25 percent and for all other drugs by 15 percent. However, if these goals are achieved, approval will still take 15 months or longer.

Both FDA and the drug industry contribute to the length of the drug approval process, and both need to work to speed it up. This report recommends ways FDA can expedite the process.

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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

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✓ The Honorable George E. Brown, Jr.
Chairman, Subcommittee on Science,
Research, and Technology
Committee on Science and Technology
House of Representatives

FSE 03506

FSE 03508

Dear Mr. Chairman:

In response to a May 9, 1977, request by the Chairman of the Subcommittee on Domestic and International Scientific Planning, Analysis, and Cooperation, House Committee on Science and Technology, we have reviewed the Food and Drug Administration's (FDA's) drug approval process.

Our review consisted of (1) obtaining the views and concerns of the drug industry, pharmaceutical associations, and other knowledgeable members of academia and FDA officials, (2) comparing drug approval procedures in Canada and eight European countries with those of the United States, (3) analyzing FDA's review process for selected new drug applications, (4) analyzing the workload of FDA physicians, chemists, and pharmacologists involved in reviewing new drug applications, (5) interviewing FDA reviewers of new drug applications for their perceptions of the drug approval process, and (6) reviewing FDA's use of scientific and management information systems in its drug approval activities.

The report includes recommendations to the Secretary of Health and Human Services. (See pp. 27, 42, and 64.) The agency was given an opportunity to comment on our draft report, and its comments are included where appropriate.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its issue date. At that time we will send copies to interested parties and make copies available to others upon request.

Sincerely yours,

Comptroller General
of the United States

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COMPTROLLER GENERAL'S
REPORT TO THE SUBCOMMITTEE
ON SCIENCE, RESEARCH, AND
TECHNOLOGY
HOUSE COMMITTEE ON SCIENCE
AND TECHNOLOGY

FDA DRUG APPROVAL--A LENGTHY
PROCESS THAT DELAYS THE
AVAILABILITY OF IMPORTANT
NEW DRUGS

D I G E S T

The Food and Drug Administration (FDA) regulates the testing and marketing of all drugs to be used by humans in the United States. In approving new drugs, FDA must carefully assess their risks and benefits to assure that the public health is protected.

FDA's approval process is, however, lengthy, and it often takes almost as long to approve an important drug as to approve drugs of less importance. FDA defines important drugs as those providing major or modest therapeutic gains over drugs already being marketed. The lengthy approval process delays the benefits important drugs can provide to the public. (See p. 4.)

The Federal Food, Drug, and Cosmetic Act requires that FDA approve new drug applications within 180 days, or about 6 months after they are filed, or give an applicant notice of an opportunity for a hearing on the application's deficiencies. The Congress considered that the 6-month time limit adequately balanced the Government's interest in having enough time to evaluate new drugs with the industry's interest in promptly marketing new products. Where more time is needed, the law permits the time to be extended by mutual agreement between FDA and the applicant. (See p. 4.)

GAO's analysis of the 132 new drug applications submitted in 1975 showed that FDA had approved 69 (52 percent) by the end of May 1979. The average approval time for these applications, which included 11 important drugs, was about 20 months--17 months of

FDA time and 3 months of industry time. Only one application was approved within 6 months. (See p. 6.)

A number of important drugs were approved in some foreign countries in less time than in the United States. With the exception of Sweden, approval times in the countries GAO visited were considerably shorter. (See p. 6.)

Some of the 14 important drugs GAO selected were available earlier in the United States than in some foreign countries--all but 1 were available in at least one foreign country before they were available in the United States. (See p. 8.)

--Disopyramide, used to treat abnormal heart rhythm, was available more than 5 years earlier in the United Kingdom.

--Propranolol, an important advance in treating high blood pressure at the time of its introduction, was available more than 7 years earlier in the United Kingdom.

--Sodium valproate, used to treat epilepsy, was available about 6 years earlier in Switzerland. (See p. 8.)

FACTORS CONTRIBUTING TO LONG APPROVAL TIMES

Both FDA and the drug industry contribute to the time it takes to approve new drugs. Industry officials pointed out and GAO's review confirmed that major factors affecting drug approval time were:

--Imprecise FDA guidelines, subject to varying interpretations.

--Scientific and professional disagreements between FDA and industry.

--Slow or inadequate FDA feedback to industry and lack of promptness in notifying drug firms of deficiencies in applications.

- Lengthy chemistry and manufacturing control reviews.
- Limited time spent reviewing and uneven workload.
- Incomplete new drug applications and industry's slow rate of resolving deficiencies. (See p. 12.)

Other factors include intense congressional and consumer scrutiny of the drug approval process, adversary relationships between FDA and the drug industry, and FDA's conservative approach to drug regulation. (See p. 30.)

FDA ACTIONS TO SPEED UP
THE DRUG APPROVAL PROCESS

FDA has initiated actions to speed up the drug approval process. It has established goals to reduce processing time over 3 years by 25 percent for important new drug applications and by 15 percent for all others. (See p. 21.)

To achieve these goals, FDA plans to issue guidelines for clinical studies, manufacturing controls, and submission of applications. In addition, it plans to streamline the review process. It should monitor these actions and revise them when necessary to assure that goals are met. Even if goals are met, the average approval time will be about 15 to 17 months.

OTHER FACTORS THAT COULD SPEED UP
THE DRUG APPROVAL PROCESS

GAO compared the U.S. drug approval process with drug approval in several foreign countries and identified policies or practices in those countries that tended to speed up approval. These practices included:

- The state of development of postmarketing surveillance systems. Widespread usage of drugs after marketing would shed evidence

on safety and efficacy which is not obtainable through the limited controlled clinical trials presently used to show safety and efficacy. If an adequate system existed and FDA had the power to expeditiously withdraw drugs in contested cases or modulate their use, postmarketing surveillance might replace certain phases of present clinical testing and thus reduce the approval process. The usefulness of FDA's present system is affected by the reluctance of physicians to report drug reactions because of a perceived fear of possible malpractice suits. (See p. 30.)

- The use of an expert committee to review and approve, or recommend approval of, important new drugs. In foreign countries the professional status of the committee lends considerable credibility to its recommendations and serves as a buffer between the regulatory agency and political and consumer advocates. (See p. 34.)
- Acceptance of foreign clinical data to demonstrate the safety and efficacy of a new drug. If FDA accepted adequate and well-controlled foreign clinical studies, important new drugs might be introduced earlier. FDA's policy on the acceptance of foreign data needs to be formally clarified. (See p. 35.)

RECOMMENDATIONS

GAO is making several recommendations to the Secretary of Health, Education, and Welfare. 1/ (See pp. 27, 42, and 64.)

1/On May 4, 1980, a separate Department of Education was created. The part of the Department of Health, Education, and Welfare responsible for the activities discussed in this report became the Department of Health and Human Services. This Department is referred to as the Department of Health, Education, and Welfare throughout this report.

The more significant recommendations are that the Secretary direct the Commissioner of FDA to:

- Monitor FDA's progress toward reducing processing time for new drug applications 25 and 15 percent over a 3-year period and revise actions when necessary to assure that these goals are met. (See p. 27.)
- Give the industry timely feedback on deficiencies in new drug applications and on instances when it is responsible for delaying drug approval. (See p. 28.)
- Expedite development of an improved post-marketing surveillance program and provide for feedback on program results to reporting physicians. (See p. 43.)
- Formally clarify FDA's policy on the acceptance of foreign data. (See p. 43.)

PENDING LEGISLATION

During the 96th Congress, two legislative proposals entitled the Drug Regulation Reform Act of 1979 (H.R. 4258 and S. 1075) were introduced. These proposals would:

- Require drug firms to establish and maintain a system for collecting and reporting adverse drug reaction information (postmarketing surveillance) to FDA. (See p. 54.)
- Provide for informal procedures for resolving scientific disagreements between FDA and drug firms. (See p. 54.)

GAO believes a number of other provisions in these proposals would shorten the time required to review and approve certain new drug applications or would improve health care for people. These provisions would:

- Reduce duplicate clinical tests on already marketed drugs. This would avoid duplicate industry testing, which wastes scientific resources, and would allow FDA to use its limited number of reviewers more effectively. (See p. 45.)
- Reduce regulation in the early phases of new drug testing. This would encourage more drug innovation in the United States. (See p. 47.)
- Accelerate approval of breakthrough drugs (major therapeutic advances). This would permit the use of these drugs much sooner than they normally would become available. (See p. 49.)
- Restrict distribution of certain drugs that are suited for a controlled environment but which would not be approved for general distribution because of the risk involved. Such restricted use would make important drugs available earlier and permit the use of some drugs that might not be available for general distribution. (See p. 51.)

AGENCY COMMENTS

The Department of Health, Education, and Welfare in its comments (see app. V) said it is aware that the evaluation of new drugs in the United States takes a considerable time. Although the agency did disagree with the basis of certain of the analyses used in the review, it agreed with most of the recommendations. The agency's comments are discussed on pages 9, 28, 43, 55, and 65.

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ABBREVIATIONS

| | |
|----------|--|
| ADP | automated data processing |
| FDA | Food and Drug Administration |
| FD&C Act | Federal Food, Drug, and Cosmetic Act |
| GAO | General Accounting Office |
| HEW | Department of Health, Education, and Welfare |
| IND | investigational new drug application |
| NDA | new drug application |

CHAPTER 1

INTRODUCTION

The Food and Drug Administration (FDA) is responsible for regulating the testing and marketing of all human drugs in the United States. Over the years, several hundred thousand prescription and over-the-counter drug products have been marketed by over 4,500 establishments. In approving new drugs for marketing, FDA must assure that the public health is protected by carefully assessing the risks and benefits associated with new drugs and making such drugs available to the public as soon as possible. FDA's legal authority and responsibility for regulating and approving new drugs is the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301).

REQUIREMENTS OF THE LAW AND IMPLEMENTING REGULATIONS

The FD&C Act and implementing regulations for the investigational use of new drugs require FDA to regulate the clinical (human) testing of new drugs. Since 1962 the act has required that, before a new drug may be introduced into interstate commerce, FDA must approve it for safety and efficacy. Before that time there was no requirement that FDA be notified that drugs were being tested on humans or that a new drug be proven effective for its intended use.

A new drug is defined by the act as any drug not generally recognized, among qualified experts, as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling. A new drug may be an entirely new substance, a marketed drug in a new formulation, or a marketed drug being proposed for a new use (that is, a use for which the drug is not approved).

The development of new drugs, which can be undertaken by a drug firm, a Federal agency, or an independent investigator, usually begins with the screening of large numbers of chemical compounds in laboratory animals for possible therapeutic activity. The sponsor then selects a few of the most promising compounds for further study. The sponsor must demonstrate the safety and efficacy of a new drug product through closely controlled clinical tests.

After completing the animal and clinical tests, the sponsor may file with FDA a new drug application (NDA), which, if approved, would permit the sponsor to market the drug. The NDA contains (1) full reports of investigations, including animal and clinical investigations, that have been made to show whether the drug is safe and effective, (2) a statement of the drug's composition, (3) a description of the methods used in, and the facilities and controls for, the manufacturing, processing, and packaging of the drug, (4) samples of the drug and components as may be required, and (5) a copy of the proposed labeling.

THE NDA REVIEW PROCESS

All NDAs are reviewed by the Office of the Associate Director of New Drug Evaluation in FDA's Bureau of Drugs. This Office comprises eight divisions, six of which review NDAs. Each of the six divisions is responsible for evaluating drugs in a particular therapeutic class or for use in a particular organ system.

To review the data submitted, FDA uses a team made up of (1) a medical officer, who reviews the clinical test results, (2) a pharmacologist, who reviews the animal test results, and (3) a chemist, who reviews the chemistry and manufacturing controls and processes. The review team may also be supported by a biopharmaceutical specialist, a microbiologist, and a statistician. A supervisory medical officer is responsible for coordinating the team's activities.

As required by the FD&C Act, within 180 days after an NDA is filed, FDA must approve it or give the applicant notice of an opportunity for a hearing on the deficiencies found. FDA may take longer than 180 days to decide on an application if the applicant and FDA agree to an additional period of time.

Since 1962, when FDA was required to regulate the testing of new drugs, it has reviewed over 13,500 applications for investigational use of new drugs. Between 1962 and 1978, FDA approved 1,000 NDAs.

PURPOSE AND SCOPE OF REVIEW

Our review was requested by the Chairman of the Subcommittee on Domestic and International Scientific Planning,

Analysis, and Cooperation, House Committee on Science and Technology, which in the current Congress was merged with the Science, Research, and Technology Subcommittee. Our review was directed at determining (1) how long it takes to process NDAs and approve drugs for marketing in the United States, (2) whether delays in approving new drugs adversely affect the introduction into the United States of important drugs that are available in other countries, (3) how FDA's drug approval process compares with those of other countries, and (4) whether FDA uses computer technology in its drug approval process.

We met with officials of 10 drug firms, numerous pharmaceutical and medical association members, and academicians to obtain their insights on the drug approval process. The drug firms visited and others we later contacted included both U.S. and foreign-based multinational firms. The firms visited were Burroughs Wellcome Co.; Cutter Laboratories; Eli Lilly and Co.; Hoffman-La Roche, Inc.; Merck, Inc.; Parke, Davis, and Co.; Pfizer, Inc.; Sterling Drug, Inc.; Syntex Laboratories, Inc.; and the Upjohn Company.

We visited nine foreign countries and obtained the views of foreign regulatory and pharmaceutical officials, medical experts, academicians, and members of medical associations concerning the similarities and differences between their drug approval processes and those of the United States. The countries visited were Canada, France, West Germany, Italy, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom. Because we did not have legal access to the records and files of the drug regulatory agencies in these countries, we obtained our information through interviews.

In reviewing the FDA drug approval process, we reviewed the legislation and FDA regulations, NDA files, correspondence, and miscellaneous records. We interviewed members of the Bureau of Drugs' management as well as 46 physicians, chemists, and pharmacologists involved in reviewing NDAs. We also contacted numerous officials of the pharmaceutical industry regarding specific NDAs.

CHAPTER 2

FDA DRUG APPROVAL

PROCESS TAKES A LONG TIME

The Congress specified in the FD&C Act (21 U.S.C. 355(c)) that, within 180 days (about 6 months) after an NDA is filed, FDA must approve it or give the applicant notice of an opportunity for a hearing on the deficiencies found. The Congress considered the 6-month time limit adequate to balance the Government's interest in having enough time to evaluate new drugs and the industry's interest in promptly marketing its new products. Where more time is needed, however, the law permits the time limit to be extended by mutual agreement between FDA and the applicant.

Our analysis of NDAs initially submitted in calendar year 1975 showed that, for those approved as of May 31, 1979, the average time from submission of application to approval was about 20 months. This included about 17 months of FDA time and about 3 months of industry time used to resolve deficiencies cited by FDA.

NDAs that were involved in the lengthy review process included drugs FDA classified as being important. FDA considers a new drug important if it provides a major or modest therapeutic gain over any marketed drugs. In many cases, FDA takes about as long to approve important new drugs as it does to approve drugs that have little or no therapeutic advantages over drugs on the market. The lengthy approval process delays the therapeutic advantages of important new drugs to the public and, according to industry officials, adds substantially to the cost of developing new drugs. One industry source advised us that, for each month a drug firm is awaiting approval of a drug, about \$200,000 is incurred for clinical studies.

A number of important new drugs were approved in certain foreign countries in a shorter period of time than in the United States. All countries we visited require drugs to be proven safe and effective. With the exception of Sweden, the approval times in the countries we visited were considerably shorter.

LENGTHY NDA PROCESSING

To determine the time taken to process and approve NDAs, we analyzed all NDAs initially submitted in the same calendar year. We chose 1975--a year that would allow us to look at what happened to a group of NDAs over time, yet recent enough to reflect current regulations and practices.

Our analysis of the 132 original NDAs submitted in 1975 showed that only 1 was approved within 6 months and 86 (65 percent) took longer than 6 months to initially review and notify the applicant of the deficiencies. A profile of the 132 NDAs is shown in appendix I.

As of May 31, 1979, FDA had approved 69 (52 percent) of the 132 NDAs. The average time to approval for these 69 NDAs, which included 11 important new drugs, was about 20 months. As stated, this represents 17 months of FDA time and 3 months of industry time. Six of the 11 important new drugs took 20 months or more. Average time to approval of the 69 NDAs varied by the NDA's therapeutic significance, chemical type, company size, or the specific division within FDA responsible for reviewing the therapeutic category of the drug; however, all categories took an average of 17 months or more. The average time to approval of each of these categories is shown in the following table.

| <u>Category</u> | <u>Average time to approval</u> | | |
|---|---------------------------------|------------|-----------------|
| | <u>Total</u> | <u>FDA</u> | <u>Industry</u> |
| | ————(months)———— | | |
| Therapeutic ranking: | | | |
| Important drugs | 21 | 19 | 2 |
| Other drugs | 19 | 16 | 3 |
| Chemical type: | | | |
| New molecular entities | 24 | 22 | 2 |
| New formulations | 17 | 14 | 3 |
| Marketed drugs | 20 | 16 | 4 |
| Size of company: | | | |
| Large (research budget more than \$30 million) | 18 | 15 | 3 |
| Medium (research budget \$10 million-\$30 million) | 17 | 15 | 2 |
| Small (research budget less than \$10 million) | 22 | 19 | 3 |
| FDA division: | | | |
| Cardio-renal drug products | 23 | 20 | 3 |
| Neuropharmacological drug products | 20 | 17 | 3 |
| Metabolism-endocrine drug products | 17 | 14 | 3 |
| Anti-infective drug products | 20 | 18 | 2 |
| Oncology and radiopharmaceuti- cal drug products | 22 | 18 | 4 |
| Surgical-dental drug products | 17 | 13 | 4 |

IMPORTANT NEW DRUGS TAKE
A LONG TIME TO APPROVE

Of the 132 new drugs submitted to FDA for approval in 1975, 69 were approved, including 11 classified by FDA as important. The 11 took from 12 to 32 months to be approved; about half took over 20 months. For example, dobutamine, a drug used to treat cardiac decompensation (a form of heart failure) was approved in July 1978, about 31 months after it was initially submitted for approval. Another new drug FDA classified as important is somatotropin. This drug, used to promote growth in children of short stature due to a deficiency of pituitary growth hormone, was approved in July 1976, about 15 months after an NDA was submitted to FDA.

For drugs approved during 1974-77, important new drugs took about as long to approve as other drugs. For example, for important new drugs approved in 1977, the average approval time was 24 months, compared to 27 months for other drugs.

Important new drugs approved in 1978 required a little less time for approval than those approved in prior years. However, the approval time for other drugs was substantially longer in 1978 (36 months) than the approval times for these drugs in prior years (a range of 21 to 27 months), as shown in the following table:

| Drugs approved during | Average number of months for approval of drugs | |
|-----------------------------|---|-------|
| | Important | Other |
| 1974 | 21 | 24 |
| 1975 | 22 | 21 |
| 1976 | 24 | 24 |
| 1977 | 24 | 27 |
| 1978 | 20 | 36 |

We selected 14 important new drugs to compare the approval time in the United States with approval times in foreign countries. Of the nine foreign countries visited, five provided us with information on their approval time for these drugs. These 14 drugs, according to FDA records, represent all the important new drugs approved by FDA during the period July 1975 through February 1978 and also approved for marketing in European countries.

Thirteen of the 14 new drugs were approved in at least one of the five foreign countries in less time than in the United States. (See app. II for the approval times of these

drugs.) For example, beclomethasone dipropionate, a drug used to treat chronic asthma, was submitted to FDA in February 1974 and approved in May 1976--27 months later. This drug was approved in a much shorter period of time in Canada, Norway, Sweden, Switzerland, and the United Kingdom. The approval times ranged from 5 months in the United Kingdom to 19 months in Sweden.

In some of these cases, an NDA was submitted to FDA before it was submitted to another country, but the drug was approved for marketing in the other country before it was approved in the United States. For example, an application for prazosin, used to treat hypertension, was submitted for approval in the United Kingdom in April 1973 and in the United States in February 1973. This new drug was approved for use in the United States in June 1976, 40 months after the NDA was submitted, and was approved in the United Kingdom in October 1973, 6 months after the application was submitted. An application for another new drug, cimetidine, used to treat duodenal ulcers, was submitted to FDA in July 1976, and 2 months later the application was submitted to the United Kingdom. This drug was approved by the United Kingdom in November 1976 and by FDA in August 1977.

Sweden and the United States had the longest average approval times for the 14 important new drugs, and the United Kingdom and Switzerland had the shortest average approval times. The average approval times for the five foreign countries and the United States are shown in the following table.

| <u>Country</u> | <u>Average time</u> (months) |
|----------------|---------------------------------|
| Canada | 16 |
| Norway | 17 |
| Sweden | 28 |
| Switzerland | 12 |
| United Kingdom | 5 |
| United States | 23 |

According to regulatory officials in the five countries, average approval times for the 14 drugs are representative of the approval times for all drugs in these countries.

Because we did not have access to drug records of the foreign countries, we were not able to determine why they approved drugs in a shorter period of time. However, there

are a number of differences between the FDA and foreign drug approval processes; these are discussed in chapter 4.

IMPORTANT NEW DRUGS AVAILABLE
EARLIER IN OTHER COUNTRIES

Although some of the 14 important new drugs were available earlier in the United States than in certain other countries, all but 1 of them were available earlier in at least one of these five countries. (See app. III for a detailed breakout by drug and country.) At the time of our European visits, Sodium Iodine I-123 was available in the United States but not in any of the five foreign countries. The remaining 13 drugs were available from about 2 months to almost 13 years earlier elsewhere than in the United States. Most of these other 13 drugs were available earlier in Switzerland and the United Kingdom.

For example, somatotropin, discussed earlier, was available in the United States in July 1976, but was available in Sweden in May 1971. Other drugs available earlier elsewhere include:

- Disopyramide, used to treat abnormal heart rhythm, was available more than 5 years earlier in the United Kingdom.
- Propranolol, an important advance in treating high blood pressure at the time of its introduction, was available more than 7 years earlier in the United Kingdom.
- Sodium valproate, used to treat epilepsy, was available about 6 years earlier in Switzerland.
- Bromocryptine was available almost 3 years earlier in Switzerland. It is used to treat an endocrine disorder of the uterus and breast, Parkinson's disease (a nervous system disease affecting older people), and acromegaly (an endocrine system disease with a particular effect on the bones).

AGENCY COMMENTS
AND OUR EVALUATION

The Department of Health, Education, and Welfare (HEW), 1/ in commenting on our draft report (see app. V), said that it is aware that the evaluation of new drugs in the United States takes considerable time. It explained that the process is lengthy because the system is deliberate and thorough; it operates on the basis of an administrative record which contains the evaluations of the data and evidence submitted by applicants.

Although HEW agreed with most of the recommendations in our report, it disagreed with the basis of certain of the analyses used in the review. HEW's specific comments in this regard are discussed below.

--HEW considers our report unbalanced because it focuses on the speed of the NDA approval process alone and does not strike an appropriate balance between adequate scientific testing of new drugs, the therapeutic needs of patients, and property rights of drug manufacturers. Moreover, according to HEW, neither the feasibility of speeding up the process with current resources nor the health risks of adopting a quicker, more superficial review process are considered in this report.

Our report does not advocate that FDA change its requirements for scientific testing or minimize the protection of patients. Such matters were not reviewed and were not included in the scope of our review. We believe that the primary responsibility for these concerns rests with the FDA Commissioner. Our focus was on the means by which the test results and other information required in an NDA were reviewed and processed. While we have suggested that FDA make its process more efficient and responsive, we are not advocating a superficial review process. With regard to speeding up the review process with its current resources, we have suggested that FDA consider the use of paraprofessionals as a means of maximizing the use of its resources. (See p. 28.)

1/On May 4, 1980, a separate Department of Education was created. The part of HEW responsible for the activities discussed in this report became the Department of Health and Human Services. This Department is referred to as HEW throughout this report.

--HEW said that, while our report discloses that drug evaluation is a lengthy process, it does not provide evidence of inordinate delays.

We did not attempt to draw the fine line between the lengthy review process and inordinate delays. The objective of our review was to determine whether the FDA drug approval review process could be improved. We made several recommendations to speed up the process (without sacrificing quality of review). HEW acknowledges that it continues to seek ways to improve its timeliness and responsiveness. In this regard, (1) HEW has directed FDA to reduce the processing time for important new drug applications by 25 percent and for all other drugs by 15 percent (see p. 12), (2) legislation has been proposed to speed up the process (see p. 45), and (3) FDA has initiated administrative actions intended to streamline and speed up the process (see p. 21).

--HEW said that our report does not describe or discuss the benefit-risk analysis of marketing drugs between countries.

Neither FDA nor foreign drug regulatory agencies document any benefit-risk analysis they might make; therefore, we were not able to make this comparison. It should be noted, however, that HEW considers its benefit-risk analysis one of the most important elements in evaluating an NDA.

--HEW said that our comparisons of the drug approval process in the United States with those of several European countries are based only on testimonial reports of interviews with foreign drug representatives and the opinions of one or two foreign drug regulatory officials.

Contrary to HEW's statement, our comparisons were based on information obtained through extensive discussions with (1) the most responsible drug regulatory officials in nine foreign countries, (2) nationally recognized physicians, pharmacologists, academicians, and researchers, (3) respected physicians of medical societies, and (4) senior officials of multinational companies. Further, the results of our interviews were corroborated when possible by published descriptions of the foreign drug approval process and analytical analysis performed and published by researchers in the United States.

--HEW stated that the sample of drugs we selected to compare with foreign countries was biased in favor

of drugs approved in other countries before they were approved in the United States. Also, no attempt was made to examine a sample of drugs approved in the United States before they were approved in foreign countries.

Some drugs, as HEW's comments indicated, may have been approved in the United States before they were approved in certain foreign countries. However, the primary objective of our review focused on the timeliness of FDA's drug approval process. In this regard, the overall average approval time for drugs in the United States was longer than in the foreign countries we visited with the exception of Sweden.

CHAPTER 3

FACTORS CONTRIBUTING TO LENGTHY

DRUG APPROVAL PROCESS

Both FDA and the drug industry contribute to the long time it takes to approve drugs; therefore, both need to work to speed up the process. FDA has established goals to reduce the processing time for important new drug applications by 25 percent and for all other drugs by 15 percent. However, even if these goals are achieved, the average time to approval of drugs will be about 15 to 17 months.

The major factors that affect the time to approve NDAs, as pointed out by industry officials and our analysis of FDA's process, include the following:

- FDA guidelines are not precise and, therefore, are subject to varying interpretations.
- Reviewers change during the NDA review, which slows the process.
- Scientific and professional disagreements between FDA and industry are not resolved quickly.
- FDA feedback to industry is slow or inadequate, and drug firms are not promptly notified of deficiencies in NDAs.
- Chemistry and manufacturing control reviews delay processing.
- Limited time spent reviewing NDAs and uneven workload slow the process.
- Industry submits incomplete NDAs and is slow to resolve deficiencies.

NEED FOR CLEARER GUIDELINES

In recent years, FDA has issued guidelines for clinical testing of individual drug classes to provide more specific guidance to drug firms. These guidelines, according to FDA, were developed with assistance from FDA advisory committees and input from industry representatives and other experts and are currently in widespread use by industry.

Other FDA guidelines, however, regarding documentation to be submitted with an NDA and formatting of such documentation are vague, according to industry officials. As a result, officials from 8 of the 10 drug firms we visited believe FDA reviewers use personal preferences and standards that differ among reviewers in determining the adequacy of documentation submitted and the manner in which it is presented. One industry official described the situation as "the target moving faster than the bullet."

Many of the 46 FDA reviewers (medical officers, chemists, and pharmacologists) we interviewed alluded to the problem of unclear guidelines when they identified inadequate information, poor organization, and use of different formats by drug firms as a main cause for delays in completing their NDA reviews. These reviewers indicated that poor organization and the different ways in which the data are presented cause them to lose time by having to look for essential data and having to reformat the data to complete their analysis.

Our analysis of NDAs submitted for FDA approval showed that FDA often requested additional information from drug firms. For example, 129 (98 percent) of the 132 NDAs submitted to FDA for approval in 1975 were recycled by FDA one or more times for additional data. Some were recycled as many as four times over a period of about 3-1/2 years. Although most deficiencies related to problems with the chemistry and manufacturing of a drug which were the most time consuming to resolve, there were also problems with the clinical data submitted.

We contacted industry officials on 20 NDAs that had not been approved as of May 1979, to determine why the applications were deficient. These officials said that the deficiencies resulted because FDA reviewers were inconsistent regarding the amount of detailed chemistry and manufacturing data they required with an NDA.

For example, one industry official said that FDA reviewers require more detail on chemistry and manufacturing controls now than before, although the guidelines for submission of such information have not changed since 1971. Regarding chemistry, this official explained that, 5 years ago, a two-paragraph description of the method of synthesis and the various drug components used was acceptable. About 3 years ago, a four- or five-page description was required. Today, some FDA reviewers require a copy of the detailed synthesis procedures used.

This official added that, in many other areas in chemistry and manufacturing controls, additional detail may be requested because reviewers interpret guidelines differently.

We analyzed 45 of the 132 NDAs in detail. As of June 30, 1978, 25 of the 45 had been approved. Forty-one of the cases were found deficient in one or more areas in chemistry and manufacturing controls. According to some drug firm officials, guidelines were not clear on what documentation was required for chemistry and manufacturing controls. Recognizing the need for clearer guidance, FDA is revising its guidelines.

NDA REVIEWERS CHANGE

Industry officials told us that sometimes FDA reviewers changed before the NDA processing was completed. This, according to the officials from 9 of the 10 drug firms we visited, has increased the time it takes to review NDAs because the new reviewer reexamines all the data and raises additional questions. Of the 45 NDAs we reviewed in detail, 17 had reviewers change during processing. In 5 of the 17 cases, the reviewers changed more than once.

We discussed reviewer changes with FDA officials. They explained that, generally, such a change occurs when a reviewer leaves FDA or when a reviewer's workload requires a change to speed up the review of pending NDAs. However, they recognized that changing reviewers is undesirable and said they try to minimize such changes.

RESOLVING SCIENTIFIC AND PROFESSIONAL DISAGREEMENTS

Officials from 9 of the 10 drug firms we visited told us that the issues raised by FDA sometimes involved areas of scientific disagreement. They said there was no established mechanism for promptly resolving these disagreements. Drug firms can request an administrative hearing to resolve such issues, but this procedure is time consuming and seldom used.

Because of their concern over damaging their relationship with FDA, industry officials did not provide specific examples of NDAs where scientific disagreements delayed the approval process. In addition, because of the technical nature of the issues discussed in correspondence between FDA and the industry, we were not able to clearly identify such examples. However, where there is disagreement, steps should be taken to try and resolve it.

FDA believes that most disagreements are resolved quickly and without rancor in meetings between reviewers and industry representatives. However, FDA advised us that the Bureau of Drugs is addressing the problem of appeals on decisions in revisions to its regulations. In addition, pending legislative bills (H.R. 4258 and S. 1075), cited as the Drug Regulation Reform Act of 1979, provide for informal, expeditious procedures for review and, if possible, resolution of scientific disagreements. The proposed legislation is discussed in chapter 5.

FDA FEEDBACK TO INDUSTRY NEEDS IMPROVEMENT

Officials from all 10 drug firms we visited said slow or inadequate feedback from FDA contributed to delays in reviewing and approving NDAs. Seven of the 10 firms considered feedback problems as the primary reason for delays. Industry officials indicated that FDA reviewers did not provide drug firms with timely feedback on deficiencies noted in their reviews of NDAs.

Industry's perception of slow feedback may be due to the fact that many FDA reviewers do not notify industry until all reviews are completed. Twenty-one (46 percent) of the 46 reviewers we interviewed said they did not notify drug firms of NDA deficiencies until other members of the review team had completed their reviews. Medical officers, chemists, and pharmacologists were consistent in this regard; 43 percent, 46 percent, and 55 percent, respectively, said they did not notify drug firms until the other two reviewers finished their reviews. In some instances reviewers completed their work 1 to 4 months earlier than other reviewers of the same NDA.

Our analysis of the 132 NDAs and the comments of FDA and industry officials indicate the need for better feedback between FDA and drug firms. FDA sends an action letter to the drug firm to approve the NDA or to formally stop its review to obtain information from the drug firm. We analyzed FDA action letters to drug firms through June 30, 1978, on all 132 NDAs. FDA sent action letters on 129 of the NDAs requesting additional information from the firms. In some cases, after receiving the firm's response, FDA sent additional action letters for still more information. In some cases, this practice was repeated four times.

Because of the technical nature of the requests, we could not determine if the drug firms fully responded to FDA's requests. It would appear from the number of exchanges that there is a need for both FDA and drug firms to make greater efforts to improve feedback; that is, for FDA to clarify what is needed and for drug firms to respond more effectively.

CHEMISTRY AND MANUFACTURING
CONTROL REVIEWS DELAY PROCESSING

FDA's review of the chemistry portion of the NDA takes longer than the pharmacological and medical reviews. According to FDA officials, much of this time, however, represents time spent by others to support the chemist's review. For example, part of this support activity involves inspecting manufacturing facilities for compliance with FDA's good manufacturing practices regulations. These inspections are performed by FDA field inspectors. Also, FDA laboratories must verify that the testing methods proposed by the drug firms are adequate to ensure the identity, purity, quality, and strength of the drug. These support activities add to the time it takes to complete the chemist's review.

In looking at the approval times for 25 NDAs, we found that the chemistry portion of the NDA, including manufacturing controls, took an average of 17 months to approve, which was about 9 months longer than it took to approve the pharmacological and medical portions. Concerned about our finding, FDA reviewed the 25 NDAs in depth and summarized the results of 7 NDAs that it believed were representative of the total group. FDA's analysis highlighted the fact that an average of 8 months of the 17 months required to approve the chemistry portion of the seven NDAs was used for nonchemist review activities, including inspection of manufacturing facilities and laboratory reviews.

These activities significantly contribute to the review time for chemistry. FDA's analysis of 14 of the 25 NDAs showed that:

- Validation of drug manufacturing methods took 3 to 4 months instead of the 45 days FDA expects for this procedure.
- Field inspections of drug firms' plants and the firms' resolution of deficiencies noted took 6 or more months in a number of cases.

FDA's analysis also showed that processing and typing of chemists' evaluations of NDAs and letters to manufacturers sometimes took more than 4 months.

LIMITED TIME SPENT REVIEWING AND
UNEVEN WORKLOAD SLOW APPROVAL PROCESS

Because of other demands on their time, reviewers spent an average of less than 40 percent of their time reviewing NDAs, and workload is unevenly distributed. According to FDA, review time could be shortened if reviewers could spend more time reviewing NDAs.

Based on our analysis of data on the use of FDA reviewers' time during an 8-week period in 1978, medical officers spent an average of 26 percent of their time reviewing NDAs and supplemental NDAs; chemists, 39 percent; and pharmacologists, 11 percent.

According to an FDA official, one of the demands on a reviewer's time is special projects. Time spent on these projects takes time away from reviewing NDAs. FDA advised us that these projects are an integral part of the overall drug review process and must be addressed by knowledgeable people---its physicians and scientist reviewers. Further, these projects include evaluating investigational new drug exemptions and supplemental new drug applications; handling safety problems with approved drugs when they occur; preparing guidelines for clinical evaluation of specific drugs alone, furnishing manufacturing and controls guidelines; establishing labeling for drug classes and specific drugs; advising drug firms on protocols to study nonprescription drugs; meeting with scientific advisory committees, industry, or other groups; and responding to congressional and other priority correspondence.

At our request, an FDA official prepared an analysis showing the estimated time reviewers were involved with special projects in 1978. Of 167 reviewers assigned in 1978, 117 (70 percent) were involved in special projects. Total estimated time committed to special projects by these reviewers was 4,248 staff-days, or about 17 percent of their time, as shown in the table on the following page.

| Type of reviewer | Reviewers | | | Staff-days | | |
|------------------|------------|------------------------------|----------|---------------|--------------------------|----------|
| | Total | Number with special projects | Per-cent | Total | Used on special projects | Per-cent |
| Medical officers | 76 | 50 | 66 | 11,000 | 2,507 | 23 |
| Chemists | 48 | 38 | 79 | 8,360 | 1,109 | 13 |
| Pharmacologists | <u>43</u> | <u>29</u> | 67 | <u>6,380</u> | <u>632</u> | 10 |
| | <u>167</u> | <u>117</u> | 70 | <u>25,740</u> | <u>4,248</u> | 17 |

Our analysis of FDA reviewers' workload showed that the workload varied widely. As suggested by FDA officials, we analyzed work assigned to reviewers during calendar year 1977. Before this, work assignments were not recorded accurately. Our analysis included 83 percent of FDA's 164 reviewers--82 percent of the 74 medical officers, 87 percent of the 46 chemists, and 80 percent of the 44 pharmacologists.

A majority of the time spent reviewing drug applications was in three areas: (1) original investigational new drug applications (INDs) and NDAs, (2) reactivated INDs and resubmitted NDAs, and (3) supplemental NDAs. Of these, original NDAs were cited by FDA officials as the reviewers' most complex and time-consuming task. Thus, we concentrated our analysis in this area.

About 50 percent of the reviewers (including medical officers, chemists, and pharmacologists) were responsible for reviewing substantially more than 50 percent of the original NDAs. Specifically, about (1) 49 percent of the medical officers were assigned 84 percent of the NDAs, (2) 45 percent of the chemists were assigned 65 percent, and (3) 46 percent of the pharmacologists were assigned 78 percent.

In many cases, reviewers with heavy original NDA workloads also carried a large load in other drug review work. For example, one of eight reviewers in one division with 22 percent of the original NDA workload was also responsible for 25 percent of the supplemental NDAs and 16 percent of the INDs in his division.

In January and February 1979, we discussed our workload analysis with Bureau of Drugs division directors. They said workload imbalances existed because some reviewers (1) were

more proficient than others, (2) participated in special projects, or (3) were supervisors who were reluctant to delegate work to others. Also, workload was unpredictable because drug firms, not FDA, control the submission of NDAs.

According to FDA officials, reviewer abilities differed based on experience. More experienced reviewers were usually assigned the more difficult NDAs and usually had a heavier workload, whereas new reviewers were usually assigned fewer and easier NDAs. According to FDA, it takes about 2 years to train a reviewer.

Differences in workload distribution were also caused by a reviewer's lack of innate ability. According to Bureau of Drugs division directors, some reviewers were just low producers. Other reviewers perform detailed page-by-page reviews, and a decision on the NDA is not made until this detailed analysis is completed. These low producers accomplished less and for practical reasons were assigned less.

Another reason for uneven workload distribution was that some reviewers with a heavy workload were supervisors who were reluctant to delegate work to others. Twenty-five percent of the supervisors were among the heaviest loaded reviewers in their division. Division directors said they have counseled some of these supervisors and hoped to see more delegation in the future.

Division directors cited the unpredictability of incoming NDAs as a major contributor to the uneven workload distribution. FDA has no control over the influx of NDAs. Because each drug firm decides when to submit NDAs, FDA cannot control the number of NDAs that will be submitted for any division during a specific period.

FDA has tried to relieve the burden of uneven workload distribution by (1) hiring outside medical experts, (2) using paraprofessionals, (3) providing on-the-job training and counseling, and (4) hiring the best qualified people available.

Division directors spoke highly of the work done by outside medical experts who were hired to supplement their staffs. Their reviews were described as timely and quality work.

FDA has used a paraprofessional to assist medical officers in one division. The paraprofessional abstracted and summarized data from NDAs, made literature searches, and helped

prepare reports. Most division directors favor a pilot program to use paraprofessionals to assist medical officers. Most medical officers we interviewed also supported the use of paraprofessionals.

In all divisions, supervisors are providing on-the-job training for less experienced reviewers and counseling low producers to improve their performance, according to division directors.

INCOMPLETE NDA SUBMISSIONS AND
SLOW INDUSTRY RESPONSE DELAY APPROVALS

The drug industry also has contributed to the delays in processing NDAs by submitting incomplete NDAs and has not always given high priority to correcting the deficiencies identified by FDA. We contacted industry officials on 27 NDAs 1/ that had not been approved as of April 1979, about 40 months after the applications were initially submitted. Generally, they agreed with the deficiencies FDA identified on the NDAs. Industry officials told us that they intended to resolve the deficiencies and resubmit 15 of 27 NDAs for FDA approval. However, for 10 of 15 NDAs, industry officials said they placed a low priority on resolving deficiencies because (1) these drugs, in their opinion, had a limited market or (2) other concerns of the firm had higher priority. In addition, our analysis showed that, for six of the NDAs, FDA had been waiting from 21 to 36 months for firms to resubmit the additional data required.

Also, according to FDA officials, the drug industry sometimes submitted incomplete NDAs. Industry officials from six drug firms confirmed this on our followup of the 27 NDAs. For example, one industry official whose NDA was deficient with respect to manufacturing data explained:

"The deficiencies in the manufacturing and control data resulted from production personnel submitting a bad application. The production personnel ignored FDA's new GMP [Good Manufacturing Practice] requirements because the 'old hands' thought the agency did not require such material in the past so they did not include the required information in the NDA submission."

1/Includes 20 of 45 NDAs described on page 14, and 7 additional NDAs that FDA had classified as important.

Another industry official said his firm submitted only one clinical study demonstrating efficacy instead of the two studies required by FDA. He said his firm did not agree with the need for performing more than one study since the drug product was marketed in four other formulations and the product's effectiveness was well known.

In the case of four of the NDAs, industry officials indicated that they had submitted incomplete NDAs because they had limited experience with FDA and did not understand its requirements.

Regarding industry's role in delaying the NDA approval process and the status of the 27 NDAs not approved as of April 1979, FDA advised us that:

"It would appear that almost half of the original NDAs submitted to FDA and initially rejected are considered by their sponsors to be so lacking in profitability, therapeutic gain, proof of efficacy, or to be otherwise unapprovable that the sponsors do not intend to pursue them further. Two-thirds of those the sponsors do consider important enough to pursue are assigned low priorities for deficiency correction even though the sponsors agree with FDA's assessment of the deficiencies. It would appear that some drug companies use FDA reviewers as sounding boards to see if they have produced an acceptable drug rather than submitting applications for only those drugs that they are really committed to marketing. This industry practice dilutes the effectiveness of the FDA review process and causes delays in approving other, more promising drugs."

FDA ACTIONS TO SPEED UP
THE DRUG APPROVAL PROCESS

Recognizing that it takes a long time to review NDAs and that the process for approving safe and effective drugs needs to be speeded up, FDA has initiated action to improve the process. In 1975, FDA established a "priority review" for important new drugs which provides for expedited reviews. The priority review, however, has not reduced the approval time for important new drugs. For example, the average approval time for important new drugs in 1978 was 20 months--about the same as it was in 1974.

In October 1978, FDA set goals to reduce the processing time for important new drugs by 25 percent and for all other drugs by 15 percent. The FDA Commissioner, in testimony before the House Subcommittee on Science, Research, and Technology in June 1979, outlined FDA's commitment when he said:

"To make our drug approval process more efficient and responsive to the public interest, FDA's Bureau of Drugs has instituted a series of procedural changes. These allow us to identify important new drugs promptly and to manage them through the investigational and pre-marketing phases to assure that they do not languish from insufficient attention by their sponsors or by FDA. We have established goals for ourselves to reduce our own in-house processing time for new drug applications in order that we make our decisions more crisply. We have pledged to reduce our processing time on all NDA's on drugs with potential for important or modest therapeutic gains by 25 percent over 3 years and by 15 percent for all other classes of NDA's over that same period."

If the processing time for important new drugs was reduced by 25 percent, it would still take about 15 months to approval.

FDA expects to achieve its goals through procedural changes, some of which were initiated in previous years. As of September 1979, many of the procedural changes had not been fully implemented.

Actions to clarify guidelines and improve communications

FDA is issuing clinical guidelines, manufacturing control guidelines, and guidelines establishing a uniform format for presenting information in an NDA. FDA recently started to revise its IND application and NDA regulations to streamline the review process and to eliminate any outmoded or unnecessary requirements to approval. In addition, FDA plans to hold face-to-face discussions with sponsors of selected drugs. The status and objectives of each of these actions is discussed below.

Clinical guidelines

In September 1977, FDA began publishing guidelines for use by drug firms in designing studies for testing new drugs in

humans. These guidelines outline the appropriate methods of study for specific classes of drugs and desirable approaches for evaluating study results. Since September 1977, FDA has published 24 of 28 guidelines covering various classes of drugs. The other four guidelines are being prepared.

FDA believes these guidelines will speed up drug development because FDA has articulated the specific principles it uses to judge the design and performance of clinical studies. When the industry properly applies these guidelines, the clinical studies will be more likely to meet FDA requirements. In addition, there should be a common basis for the FDA medical reviewer to discuss deficiencies in design and performance with the drug firm.

FDA officials told us that the use of clinical guidelines is voluntary. Although FDA does not know how many drug firms use the guidelines, the officials said the guidelines have been useful in discussing proposed clinical trials with industry officials. They also said that the clinical data have been easier to review when industry followed the guidelines.

Although FDA had issued guidelines for 24 categories of drugs, NDAs covered by these guidelines were not submitted during our review. We believe clinical guidelines should help the industry understand FDA's requirements and reduce the deficiencies in clinical study data submitted with NDAs.

Manufacturing guidelines

FDA has advised us that it recognized the need to update guidelines for submission of data regarding chemistry and manufacturing controls and is working to develop new guidelines. FDA explained that changing technology and the increasing complexity of new drugs is a factor in the increasing requirements for details regarding chemistry and manufacturing controls. Many drugs are manufactured through complex synthetic processes and are analyzed with technology and methods that did not exist a decade ago. Thus, while the guidelines for the kinds of manufacturing and controls data may not have changed since 1971, the nature of those data have changed as technology of drug manufacturing, quality control, and analysis have changed.

FDA has been working to revise its 1971 manufacturing control guidelines since 1977. FDA plans to publish a series of seven guidelines involving various aspects of the manufacturing and control requirements for an NDA. The first

of these guidelines was published in November 1978, and the other six were in various stages of completion in December 1979. No target dates, however, had been established for publishing these guidelines.

FDA believes the manufacturing control guidelines will clarify the type of information FDA needs to determine that a sponsor can adequately produce a drug product. The new guidelines will be more detailed than the 1971 guidelines.

The importance of clarifying the manufacturing control guidelines is indicated by the fact that more than 90 percent of the NDAs are deficient in this area and that the chemistry and manufacturing control portions of an NDA often take substantially longer to approve. FDA believes, and we agree, that these guidelines should improve the quality of NDAs submitted by drug firms and reduce the reviewers' subjective interpretations of the amount of detail required to approve an NDA. We believe, however, that FDA needs to establish an early target date for publishing these guidelines.

Formats for NDA data presentation

FDA plans to develop a standard format for presenting data in an NDA submission and has enlisted the support of industry representatives to achieve this. In December 1978, FDA asked the Pharmaceutical Manufacturers Association to propose standard formats and data presentations for various pharmacological drug categories. The Association had not completed this task as of December 1979. FDA will consider these proposals in its final standard, which it expects to develop during 1980.

FDA officials told us that standard formats would reduce the agency processing time by allowing reviewers to find information faster. The formats will enable reviewers to become familiar with one presentation scheme, thereby minimizing the time needed to locate information.

Pharmaceutical Manufacturers Association officials said they also believe that standard formats for data presentation will reduce the time FDA needs to complete its review of NDAs. These officials, however, indicated that industry officials may be reluctant to adopt a standard format because some drug firms have more confidence in the methods they have used successfully in the past.

Conferences

In November 1976, FDA formalized its policy for initiating conferences with drug firms to discuss the results of early testing of promising new drugs as a means of accelerating the availability of drugs that offered important therapeutic gains. Drug firms producing drugs not considered as important new drugs can also request conferences to obtain specific guidance on their product development.

FDA's objective in meeting with drug firms is to provide more specific guidance on developing adequate, well-controlled studies for therapeutically important drugs to ensure that they clearly demonstrate a product's safety and efficacy. Because these conferences consume large amounts of the agency's limited time and resources, FDA officials do not consider it feasible to require them for all NDAs.

This policy was first implemented in January 1978; as of October 1979, 17 conferences had been held. FDA officials who participated in these meetings were encouraged by the results and the agreements reached. However, the officials were not able to say whether the desired improvement in NDA submissions would result since applications for the drugs covered by these conferences had not been received.

The guidelines discussed earlier, together with these conferences, should provide a clearer understanding of FDA's requirements for clinical studies and should make the NDA approval process more efficient.

Action to streamline FDA's review process

In addition to clarifying its guidelines and striving to communicate better with the drug industry, FDA has initiated actions to streamline its review process and assure better coordination of its review activities. Several of these actions focus on speeding up review of the chemistry and manufacturing portion of an NDA.

Early submission of chemistry and manufacturing data

Beginning in December 1978 FDA requested that industry submit during the final phase of clinical testing data on the manufacturing control aspects of the chemistry portion of NDAs

for important new drugs before the clinical testing was completed. Previously, such information was submitted with an NDA after clinical testing had been completed. FDA expects the early submission of manufacturing control data to speed up the approval of important new drugs by identifying deficiencies before a formal NDA is submitted.

As of August 1979, FDA had requested and received a submission of manufacturing control data on one important drug before an NDA was submitted. In addition, drug firms voluntarily submitted similar data on two other drugs that were not classified as important. According to FDA officials, they will normally limit early submission of such information to important new drugs.

Because most NDAs we reviewed were, in FDA's opinion, deficient with respect to chemistry and manufacturing data, this portion of the NDA took substantially longer to approve than the medical and pharmacological portions. Therefore, we believe that early submission and review of the chemistry and manufacturing data should help speed up the approval of important new drugs.

Coordination of chemistry review activities

In April 1979, FDA initiated actions to improve the timeliness of plant inspections by FDA field inspectors and verification of testing methods by FDA laboratories. FDA officials told us the agency had improved the coordination between plant inspection activities and the reviews by chemists. Also, to reduce delays in verifying testing methods, FDA officials said they have arranged to use additional FDA laboratories for this purpose. Since these support activities to the chemist's review accounted for 40 percent of the time FDA required to approve the chemistry portion of NDAs, better coordination of plant inspections and the use of additional laboratories should permit more timely completion of the chemistry review.

Other actions

To further streamline its NDA review process, FDA officials told us they have taken steps to

--hold monthly meetings with NDA reviewers and managers to discuss specific problems delaying the review and approval of promising new drugs,

--speed up the routing of NDA applications to appropriate reviewers, and

--reduce administrative processing time.

CONCLUSIONS

The process for approving NDAs takes a long time and needs to be improved. FDA has recognized this and has made a commitment to speed up the process. The actions FDA has proposed, when fully implemented, should help solve the problem. However, even if FDA meets its goal to speed up the process, the average time for approval of new drugs will still take about 15 months. Because some of these actions have been under consideration by FDA for a number of years and have not been fully implemented, FDA needs to establish firm target dates for their implementation. Also, FDA should monitor the impact of these measures to assure that each is achieving its desired effect and to determine if additional measures are necessary.

On-the-job training and counseling now being provided should help less experienced reviewers and low producers to become more proficient and assume a greater share of the workload. To further increase review capacity, paraprofessionals should be used to the extent practicable.

Because an NDA approval involves both FDA and the drug industry, drug firms must also commit themselves to speeding up the process by submitting complete NDAs and promptly resolving deficiencies FDA identifies. We believe FDA should provide drug firms with timely feedback on deficiencies in NDAs and on instances where they have delayed the approval process.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to:

- Monitor FDA's progress toward achieving the goals of reducing processing time for new drug applications 25- and 15-percent over 3-year period and revise its actions when necessary to assure that these goals are met.
- Establish additional goals until the statutory 6-month time period is achieved or propose to the Congress that it revise the 6-month time frame.

- Use paraprofessionals to assist reviewers, particularly those with heavy workloads.
- Give the industry timely feedback on deficiencies in NDAs and instances where it is responsible for delaying approval of new drugs.

AGENCY COMMENTS AND
OUR EVALUATION

HEW agrees with the need to monitor the effect of FDA actions in reducing its NDA processing time. HEW said it established its goals of reducing NDA processing time 2 years ago and has required FDA to submit reports on progress and corrective actions whenever necessary to assure its goals are met. According to HEW, FDA is on schedule in meeting its goals.

Regarding the recommendation that HEW establish additional goals until the statutory 6-month time period is achieved or propose to the Congress that it revise the 6-month time frame, HEW in its response elected the second option. However, if HEW is not successful in convincing the Congress to extend the statutory time period, then HEW should establish additional goals to try to achieve the statutory 6-month time period.

HEW also agreed with the principle of giving timely feedback to industry on deficiencies in NDAs and indicated this is being done through deficiency letters during the review process and will be further addressed when the investigational new drug and NDA regulations are revised.

HEW, however, did not agree to notify industry on instances where industry is responsible for delaying the approval process. HEW said that FDA has no legal authority and little leverage to force applicants to make speedy corrections of deficiencies and that FDA should not interfere with industry's decision to delay in responding to the deficiencies.

Deficiencies, such as obvious omissions of data from an application or lengthy industry response times causing reviewers to refamiliarize themselves with an application, waste reviewers time and delay the approval process. We believe notifying industry officials of instances where they have obviously contributed to delays in NDA approvals will remind industry officials that they are sometimes responsible for extending the approval process they criticize. Moreover, industry officials have told us that they would favor such feedback from FDA.

HEW did not agree with a proposal in our draft report to minimize the involvement of reviewers in special projects because the "special projects" we identified are an integral part of the overall drug review process. HEW pointed out that reviewer involvement in these activities assures consistency and continuity of the agency's activities. We recognize the need for and validity of these projects. Our concern was the impact these activities had on reviewers' time. In view of FDA's comments concerning the possible use of paraprofessionals, as discussed below, and the potential this has for increasing the time reviewers can devote to NDAs, we have deleted this proposal.

HEW indicated that it is making a feasibility study to determine the usefulness of paraprofessionals and that it is training six technicians to assist reviewers. After evaluating the results of these efforts, it will decide on the use of paraprofessionals. We believe that use of paraprofessionals could help to alleviate the demands on reviewers time and to minimize the impact of reviewer involvement with special projects on NDA reviews.

CHAPTER 4

DRUG APPROVAL PROCESSES:

UNITED STATES COMPARED TO FOREIGN COUNTRIES

As discussed in chapter 2, four of the five foreign countries on which we had data generally approved drugs for marketing faster than the United States. A direct comparison of the drug approval processes was not possible because of the differences in the countries' social, political, and legal systems.

FDA officials have articulated a number of basic differences in the philosophy and style of government between the United States and other countries that influence the drug approval process in this country. These basic differences include the openness of our governmental process, which is conducted on the basis of documented evidence and with proper procedural protection for the rights of all parties; the right of a petitioner to sue the government as a way of resolving differences of opinion between the petitioner and the government; and the necessity for public and congressional oversight over government programs in the United States.

However, certain factors peculiar to foreign countries tended to speed up the drug approval process. These included the reliance placed on postmarketing surveillance, the role and use of committees of experts, the degree of acceptance of foreign clinical studies, and the extent of government control over marketed drugs.

Factors peculiar to the United States that seemed to slow the approval process, in addition to intensive congressional and consumer scrutiny, included the adversary relationship between FDA and the drug industry and a conservative approach to drug regulation.

Other elements of foreign systems included restricted distribution of drugs and recertification of marketed drugs after a fixed period. Their impact on the approval process for drugs was unclear.

POSTMARKETING SURVEILLANCE

A major advantage of an effective postmarketing surveillance system is that it would represent a study of the real world of medicine and disease as opposed to the experimental

setting of controlled clinical trials used to assess safety and efficacy. Because of widespread use after marketing, it would be possible to observe the rarer adverse effects which could go undetected in controlled clinical studies because of the limited number of persons involved, as well as provide more information on the incidence of adverse reactions identified in clinical trials. Unanticipated benefits of the drug's uses might also be observed through widespread exposure to the drug.

If an adequate postmarketing surveillance system existed and FDA had the authority to expeditiously withdraw the drug in contested cases or modulate its use, such a system could replace certain phases of present clinical trials and thus reduce the drug approval process. The usefulness of FDA's present system is affected by the reluctance of some physicians to report drug reactions because of a perceived fear of possible malpractice suits.

Drug regulatory officials of the United Kingdom told us that their confidence in their postmarketing surveillance system is one factor that permits them to approve drugs as quickly as they do. According to these officials, they feel confident about releasing a new drug with less extensive clinical trials than required in the United States because they are able to monitor the drug's effect after marketing.

The postmarketing surveillance systems of the United Kingdom and the United States are based primarily on spontaneous reporting from physicians, hospitals, and drug firms. However, there are key differences in the extent of physician participation. Physician participation is affected by the amount of feedback provided to physicians and their perceptions of the degree of confidentiality provided to them.

Virtually all the foreign countries we visited, including the United Kingdom, have national health care systems with governmental controls which may facilitate the review of medical documents by government authorities, thus making the reporting of adverse reactions more likely. The United Kingdom has a formal followup procedure for adverse drug reaction reports and is able to protect the confidentiality of the reporting source. Because of this, according to a United Kingdom drug regulatory official, physician participation is greater in the United Kingdom than in other countries.

United Kingdom drug regulatory officials told us that the reports from this voluntary spontaneous reporting system

alone would be of little use if it were not for a network of doctors who work for the National Department of Health and Social Security. These doctors follow up on about 5 percent of the serious adverse drug reactions to ascertain if there is a causal relationship between the reaction and the drug. The doctors also conduct special studies on certain problems suspected but not clearly indicated by the reporting system.

In the United Kingdom, physicians and dentists report proportionately more adverse drug reactions than their counterparts in the United States. For example, although there are six times more physicians and dentists in the United States, the number of adverse reaction reports submitted in the two countries was about the same.

The United Kingdom officials also attribute some of their success with physician participation to feedback of information about adverse drug reactions, which has generated an awareness of drug-related events. According to a 1978 joint FDA and National Bureau of Standards study, the United Kingdom's Committee on Safety of Medicines, which is responsible for collecting adverse drug reaction information, corresponds extensively with individual physicians. The Committee sends information to physicians summarizing adverse drug reaction data accumulated on various drugs in which they may have an interest. In addition, the study notes that the United Kingdom makes greater use of medical and scientific journals than does the United States to provide adverse drug reaction information to the medical profession.

West Germany and Sweden also provide feedback to physicians on adverse drug reactions reported under their post-marketing surveillance systems and have greater physician participation in their systems than does the United States. West Germany, like the United Kingdom, uses personal correspondence and scientific journals to provide feedback to physicians. Sweden uses a computerized system to provide this feedback.

According to the FDA and National Bureau of Standards study, FDA has done little in the way of providing feedback to reporting physicians and hospitals. The FDA Drug Bulletin (a bimonthly pamphlet of drug-related information sent to physicians and other health professionals) and "Dear Doctor" letters, which are sent to physicians when serious problems are noted, have been used in a limited way to provide feedback.

Physician participation in the United Kingdom and other countries is further enhanced by the ability of these countries to protect not only the source of adverse drug reaction information but all adverse drug reaction information. Laws in Sweden and certain other foreign countries permit the government to protect such information from public disclosure.

After an extensive review of existing postmarketing surveillance systems, the Joint Commission on Prescription Drug Use made the following comments on liability concerns of health care providers in its final report submitted in January 1980.

"* * * one failing of present PMS [postmarketing surveillance] efforts is the inability to enlist widespread cooperation of physicians in voluntarily reporting drug use and effects. A variety of explanations has been offered to the Commission on causes for this lack of voluntary reporting * * *. One persistent theme is that physicians and hospitals fear increased medical liability if they report their drug experiences * * *. Although no one has suggested that if medical liability fears are removed, the problem of voluntary reporting would be solved, it has been suggested that if medical liability fears are not alleviated, the problem in voluntary reporting will be unsolved * * *."

The Commission's concern in this matter was sufficient to cause it to recommend a limited shield law to prevent the admission as evidence in a medical product liability action of identifiable information submitted voluntarily to a post-marketing surveillance organization.

Under foreign health care systems, governmental authority over reimbursement for salaries and drugs makes it easier to control drug distribution and utilization. Under such systems, the country may be more likely to approve drugs, knowing that the use of these drugs can more easily be restricted through the government's distribution and reimbursement authority should adverse reactions occur.

There is, of course, some variance in the extent of government control among the different countries. In Norway, for instance, all residents are covered by a national health

insurance program. The government exercises tight control over both the pricing and distribution of drugs. Norwegian officials advised us that such control allows them to immediately withdraw drugs from the market if necessary.

This is very different from the prevailing situation in the United States, where in the absence of voluntary withdrawal by a company, the Government can exercise only limited economic pressure and does not have effective control over the distribution or fast withdrawal from the market of marketed drugs in situations where withdrawals are being contested.

USE OF EXPERT COMMITTEES IN THE DRUG APPROVAL PROCESS

The drug regulatory bodies in the United States and in most foreign countries we visited recognized the value of medical experts and used them in the drug approval process. The use of the committees differed between the United States and foreign countries because of the responsibilities given to them by law. Also, the foreign countries and the United States vary in the frequency of meetings and use of expert committees. According to European regulatory and industry officials, using a committee of experts insulates the regulatory authority from public criticism, gives credence to the final decision, and expedites the review and approval of drugs.

Some European committees of experts are mandated to review all drug applications and either approve a drug when it is shown to be safe and efficacious or recommend to the regulatory agency that a drug should or should not be approved. In three countries--the Netherlands, Norway, and Sweden--the committees had been given the responsibility to make the decision to approve, reject, or withdraw a drug. The United Kingdom's committee only advises the government agency on the safety and efficacy of a drug; however, we were told that its recommendations have always been followed.

At FDA, committees are used to provide advice on problems or questions FDA may have concerning selected drug applications. However, applications are not submitted routinely to the committees in the United States as they are in foreign countries. FDA has sole responsibility for making a decision on an application based on the scientific data submitted and any advice from the expert committee.

The Director of the Bureau of Drugs said that in Europe the decisionmaking responsibility for drug approval is shared by the committee of experts. In the United States, FDA assumes full responsibility for the decision and is, accordingly, more deliberate in its decisionmaking process. Also, FDA tends to require more documentation than expert committees might require to arrive at a decision.

In most European countries we visited, all new drug applications are reviewed by expert committees, and the committees meet much more frequently than those in the United States. In the United States, however, expert committees review only selected applications, and the committees meet at irregular intervals, some no more than twice a year. The long interval between meetings, according to one industry official, can delay the processing of NDAs.

ACCEPTANCE OF FOREIGN DATA

If a country were to accept adequate, well-controlled clinical studies from another country in support of safety and efficacy, a drug might be introduced earlier in that country. The acceptance of foreign clinical data varies from country to country. Some countries may accept foreign clinical studies without domestic verification, depending on the source. Others generally accept foreign clinical data only if domestically verified. FDA's policy for acceptance of foreign clinical data has not always been clearly understood.

Foreign clinical study data are accepted by most foreign drug regulatory agencies we visited as evidence of a drug's safety and efficacy if the studies are well-conceived, well-controlled, performed by qualified experts, and conducted in accordance with acceptable ethical principles. Domestic verification is sometimes required. According to foreign government officials, the degree of additional domestic verification depends on such factors as the source of the original clinical trials, since medical practices and hereditary, dietary, and other factors may be different from those of the registering country. Some countries--the Netherlands, Norway, and Switzerland--accept foreign data submitted without domestic verification depending on the source. Other countries--Sweden and the United Kingdom--will normally request some domestic verification.

According to FDA's 1975 regulations concerning acceptance of foreign data, FDA will accept foreign clinical data to

supplement full-scale, adequate, and well-controlled clinical studies. FDA requires domestic verification with at least one well-controlled study, unless the disease under study does not occur significantly in the United States, because of differences in medical practices, and dietary and hereditary factors. FDA officials advised us that deficiencies in medical practice, population differences, if any, and prudence dictate that some experience through domestic clinical trials is necessary for the drug to be properly labeled for adequate directions and use. This position was further clarified in an April 1977 internal FDA memorandum. This memorandum states that generally FDA should require at least one domestic study for verification. However, no official formal written clarification was made to drug firms by FDA.

FDA officials advised us that, in recent years, an increasing amount of foreign clinical data has been submitted and accepted as support for an evaluation of safety and efficacy. FDA advised us that, of 129 NDAs approved during the past 5 years that were classified as new molecular entities or new salts, esters, or derivatives, 61 contained information from foreign studies and 20 contained foreign clinical data considered to be significant and/or pivotal for approval.

Although FDA may have accepted, in some cases, foreign data as pivotal evidence of the safety and efficacy of a drug, its policy in this regard is not clear. Officials of the drug firms we visited indicated that FDA would not accept foreign data as primary pivotal evidence, and required that the safety and efficacy of a drug be supported on the basis of duplicate domestic studies. FDA's Director of the Bureau of Drugs stated that FDA has had a reputation for not accepting foreign data. We believe FDA needs to formally clarify and communicate its policy on the acceptance of foreign data.

EFFECT OF CONGRESSIONAL AND CONSUMER SCRUTINY ON THE DRUG REGULATORY PROCESS

In the European countries we visited, drug regulatory officials told us there was no direct parliamentary or consumer scrutiny on the drug regulatory process. When a parliamentary body wishes to inquire about issues concerning drug regulatory policies, procedures, or decisions, drug regulatory officials are not required to appear before the parliament and thus are not subjected to parliamentary pressures. Rarely, if ever, is the regulatory agency's

director or any of its employees asked to appear before the parliament. Instead, the minister of health, who is a member of the parliament, responds to inquiries from parliament on drug regulatory matters.

Foreign drug regulatory officials advised us that members of parliament in their countries, for the most part, believe that the regulatory agency has primary responsibility for regulating drugs and that parliamentary involvement should be minimal.

FDA's drug regulatory process comes under intensive congressional oversight and scrutiny by consumer-oriented organizations. Officials of many U.S. drug firms told us that congressional and consumer scrutiny tends to slow FDA's drug approval process.

The FDA Commissioner, in testifying in June 1979 before the House Subcommittee on Science, Research, and Technology on the FDA drug approval process, spoke of the influence of the openness of the drug approval process in the United States. He said that:

"* * * contributing to the deliberate nature of the drug approval process in this country is the increasing insistence on openness and due process by all interested parties. Although not peculiar to drug regulation, the emphasis on openness in drug decisions is probably as great as in any other area of public concern. The most obvious manifestations of public demands for openness and due process include: open meeting of FDA drug advisory committees; geometric rise in FDA freedom-of-information requests; mounting numbers of consumer and industry petitions; requests for hearings; law suits demanding action or challenging Agency decisions on drugs; and aggressive oversight hearings by the Congress. Although these factors unquestionably militate against speedy drug approvals, we generally regard them as healthy trends that produce valuable intangible benefits such as greater public participation and understanding of drug benefits and risks."

According to FDA officials, in the late 1960s there were congressional hearings critical of FDA's handling of NDAs on

selected drugs still being reviewed by FDA. These officials said that, at that time, congressional oversight had been leaning toward not approving drugs because of the concern about the potential harm to the public. They added, however, that the current Congress appears to have an advocacy role on the side of approving more drugs. In addition, a rather well-developed consumer-oriented movement exists in the United States. In other developed countries such consumerist activities in the drug regulation area are almost nonexistent.

FDA officials said that the current concern of consumer-oriented organizations is toward the safety of already marketed drugs. They said there have been no great pressures from consumer groups on the new drug approval process except in a case involving sodium valproate, a drug to treat epilepsy. The Epilepsy Foundation of America influenced FDA to compel the drug manufacturer to submit an NDA. The Foundation heightened the priority of this drug for FDA's approval process.

According to FDA officials, the provision in the Drug Regulation Reform Act of 1979 that would require FDA to hold public hearings on pending NDAs and release test results submitted with the NDAs to the public would open FDA to more consumer pressure during the approval process and lengthen the review process. These officials also maintain that the more scrutiny (negative or positive) there is, the longer the drug approval process will take, because such scrutiny necessitates greater documentation.

These officials also said that congressional scrutiny is built into our political regulatory system and that congressional hearings in the late 1960s and early 1970s set the general tone for agency officials and reviewers, causing FDA to become very cautious and conservative in the drug review process. According to one FDA official, "FDA has become very careful and the process is highly documented and slow." They said this has affected the amount of detail required from industry in support of a drug's safety and efficacy.

RELATIONSHIP BETWEEN GOVERNMENT AND INDUSTRY

The relationship between drug regulators and drug industry officials differs between foreign countries and the United States. According to foreign drug regulatory and industry officials, a cooperative relationship exists between the government and the industry. Some foreign

regulatory and industry officials believe that an adversary relationship exists between FDA and the pharmaceutical industry, which results in a lack of open scientific discussion and impedes the drug regulatory process.

Most foreign drug industry officials explained that they have easy access to British, West German, Swiss, Norwegian, and Swedish experts and drug regulatory officials for frequent and open scientific discussions off the record. According to these officials, scientific discussions address the tests necessary for approval and other difficulties, and in their opinion assist in developing a framework for clinical trials.

American drug firm officials told us that FDA appears to favor an adversary relationship with industry. Bureau of Drug reviewers, according to these officials, review an application with the attitude that there are errors in the application and that they must find them. This adversary attitude is compounded by a communications problem between FDA and industry. According to drug firm officials, FDA has become increasingly inaccessible. One drug firm official told us "Industry is becoming more isolated from FDA. Bureau of Drug reviewers will not use phones to ask us questions they have on an NDA." Another drug firm official, in comparing FDA reviewers with their European counterparts said, "Medical officers are a lot more open and frank in Europe. As a result, they are able to resolve problems with NDA submissions in a more timely manner in Europe."

An official of the Pharmaceutical Manufacturers Association said that many in the industry had referred to the relationship between FDA and the drug industry as an adversary one. He added that he felt such a characterization unfortunately was still true today but hoped it would improve.

TREND TOWARD STRICTER REQUIREMENTS

Despite the differences between drug regulation in the United States and other developed countries previously discussed, most of these countries have followed the lead of the United States with a stringent philosophy of drug development and testing. Foreign industry and drug regulatory officials said that the recent trend in drug regulatory processes is to require more studies in accordance with the changing state of the art. This is due to the increased awareness of carcinogenicity, mutagenicity, and teratogenicity and their relationship with drugs.

FDA has long been considered a conservative regulatory agency and a forerunner in establishing regulatory requirements. However, the United Kingdom, because of increasing discussions on carcinogenicity, is now requiring long-term animal testing--not an FDA requirement--before permitting the testing of a drug in humans. Sweden requires 2-year carcinogenicity studies. The Swiss authorities are requiring more carcinogenicity, mutagenicity, and teratogenicity tests for new drugs.

The multinational pharmaceutical manufacturers we visited said they prefer general testing and approval requirements, which allow their scientists to use scientific judgments in researching, developing, and supporting a drug's safety and efficacy. They believe that stringent requirements delay the approval of drugs by several years and add to the cost of the already expensive new drug development process.

The FDA Commissioner testified at the June 1979 hearings before the House Subcommittee on Science, Research, and Technology that FDA was undertaking certain initiatives aimed at fostering international cooperation. These included a meeting between the Director of the Bureau of Drugs and drug regulatory officials of the European Economic Community to discuss ways in which uniform international requirements can be established. In addition, in 1980 FDA, in cooperation with the World Health Organization, will host a meeting of drug regulatory officials from around the world to produce a more coherent framework for international drug relations.

RESTRICTED DISTRIBUTION OF DRUGS

United Kingdom officials indicated that their country is able to use more flexibility than the United States. We were advised, for example, that, in approving a drug for marketing in the United Kingdom, the agency can restrict or limit the drug's use in various ways. It may, for instance, limit the use of the drug to a hospital setting or restrict prescribing authority to certain types of medical specialists. This flexibility enables the drug agency to authorize the marketing of a drug that it might not otherwise be willing to approve without additional study.

In the United States, FDA cannot approve an NDA conditionally on the fact that it must be distributed to certain physicians or used only in certain controlled settings. As discussed in chapter 5, the proposed drug regulation reform act would permit restricted distribution of certain drugs to

a controlled environment to reduce the risks associated with the drug.

LIMITED PERIOD OF DRUG REGISTRATION

In four of the eight European countries we visited, the drug approval period is limited to 5 years. If a drug firm wishes to continue marketing its products, it must make a resubmission, which may require submission of updated safety and efficacy data.

The United Kingdom has appointed a panel of experts, the Medicines Commission, which periodically reviews marketed drugs to determine whether they continue to be appropriate for marketing. The Commission reviews the country's experience with the drug and any adverse side effects resulting from its use.

In Switzerland, the drug is also approved for a 5-year period. An unscheduled revision may be carried out at any time, particularly when there is evidence of undue side effects. A Swiss official viewed the resubmission not merely as a formality, but as a complete review of the data accumulated during this period, particularly as concerns efficacy, toxicity, and side effects.

By West German law, a new drug application is required to be reviewed every 5 years by the regulatory agency for new registration. By this time the regulatory agency has had experience with the drug being on the market. As a result, the agency decides whether to (1) remove the drug from the market, (2) continue to allow it to be a prescription drug, or (3) make it available as an over-the-counter drug.

The Director of the Bureau of Drugs, in commenting on problems facing drug regulatory bodies, said:

"The administrative approval of new drug applications, and the use of innovative approaches to Phase IV testing during the early marketing phase, would be much easier if approval were granted for a finite period of time, perhaps every five years."

CONCLUSIONS

Certain critical elements of the U.S. postmarketing surveillance system do not compare favorably with those of some European countries. This is partly rooted in the fear on the part of U.S. physicians of the possibility of malpractice actions resulting from their reporting adverse drug reactions. Another reason appears to relate to the limited feedback to physicians reporting adverse drug experiences.

The use of an expert committee in many European countries serves as a buffer between the drug regulatory agency and political and consumer advocates. As a result of the committee's professional status, its recommendations have considerable credibility and are almost always accepted.

FDA's formal policy on acceptance of foreign data does not appear clear. As a result, there is some uncertainty as to whether and to what extent foreign data are being used in FDA's drug review process.

FDA, unlike some of its European counterparts, does not have the authority to approve the marketing of drugs with restrictions as to who may use a drug and where it may be used. Such restricted use may make important drugs available earlier. Because these drugs would be used in a controlled environment, monitoring of the risk would continue, and unexpected risks associated with mass distribution of these drugs would be minimized.

Although some foreign countries had a relicensure requirement, the United States has no requirement for limiting use of a drug for a prescribed period of time. In the United States, drugs, once marketed, are available indefinitely unless definitive evidence is presented that a drug is unsafe or ineffective. We were not able to determine from information provided by foreign regulatory officials the impact of the relicensure requirement on their drug approval processes.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary require the Commissioner of FDA to:

- Expedite development of an improved postmarketing surveillance program and provide for feedback on program results to reporting physicians.
- Formally clarify FDA's policy on the acceptance of foreign data.

AGENCY COMMENTS
AND OUR EVALUATION

HEW agreed with the need for expediting development of an improved postmarketing surveillance program and providing feedback on the results of the program to reporting physicians.

According to HEW, FDA has made considerable progress and improvements in its postmarketing surveillance system in recent years. HEW said that since 1977 FDA has engaged in a joint venture with the National Bureau of Standards to determine the best method for identifying adverse drug effects within the first 5 years following approval.

HEW said FDA has established registries of eye and liver reactions to drugs; increased its activities to collect information about drug reactions through the Boston Collaborative Surveillance Program, which is an intensive hospital surveillance project; and supports other intensive surveillance and event monitoring systems through extramural contracts. The information derived from these sources is essential in assessing the risks associated with drugs and in determining whether such risks outweigh the drug's benefits. Other recent FDA efforts include (1) monitoring medical literature and publishing alerts of adverse drug effects, (2) analyzing and publishing drug use trends, and (3) increasing intramural activity to gather and disseminate information about adverse drug reactions.

Regarding feedback to physicians, HEW said health professionals who report adverse drug reactions are given feedback in the form of a letter and a computer printout of other reactions reported on the same drug.

HEW also agreed that FDA should formally clarify its policy on the acceptance of foreign data and said that FDA would issue a statement to clarify its policy.

In a draft of this report, we proposed that the Congress modify the FD&C Act to protect the confidentiality of drug

experience reports submitted to FDA. HEW said that our draft report was in error in stating that the identity of patients, reporting physicians, hospitals, or clinics is currently disclosable under the Freedom of Information Act. According to HEW, contrary to the view stated in the draft report, adverse reaction reports sent to FDA are maintained in the most confidential manner as required by the Privacy Act. Although summary data are available under the Freedom of Information Act, material sent to the public contains no identifying information.

In view of HEW's comments--which are contrary to information we received from FDA personnel during our review--we have deleted our proposal.

The draft report sent to HEW also contained a proposal that the Congress modify the FD&C Act to have a singular committee with the responsibility to review, approve, or recommend approval of all important drugs, using experts who may have a vested or financial interest in a drug firm as nonvoting committee members.

HEW disagreed with our proposal and explained that there are basic differences in the philosophy and style of government between the United States and other countries that employ expert committees to judge which drugs may be marketed and which may not. According to HEW, such a system offers no advantage in the United States over the present system and presents several disadvantages. In the United States three factors make the situation different than in other countries: (1) regulatory decisionmaking is conducted in the open on the basis of documented evidence and with proper procedural protections for the rights of all parties, (2) petitioners before the Government have the right to sue the Government to resolve differences of opinion, and (3) public congressional oversight over Government programs is common. HEW said these factors would prevail in this country and influence the drug approval process even if a single prestigious committee were established to review and approve drugs. Thus, HEW does not believe such a committee would speed up the drug approval process. Based on HEW's comments, we have deleted the proposal.

CHAPTER 5

PROPOSED LEGISLATION

During the 96th Congress, two legislative proposals entitled the Drug Regulation Reform Act of 1979 (H.R. 4258 and S. 1075) were introduced. Both proposals would make substantial changes in FDA's statutory authority for the regulation of drugs. H.R. 4258 is a complete revision of the FD&C Act, while S. 1075 would (1) retain certain provisions of the original act, (2) modify some provisions, and (3) add provisions to make the drug approval process more efficient and effective. Our comments on the provisions relating to the subject areas of our review should be helpful to the Congress in considering the proposed legislation. These provisions would (1) favorably affect health care, (2) speed up the drug approval process for certain drugs, and (3) improve the drug approval process.

REDUCING DUPLICATE CLINICAL TESTS ON ALREADY MARKETED DRUGS

Both proposals should reduce the need for duplicate tests on marketed drugs. The usual procedure for approving a new drug for marketing in the United States is for a drug firm to develop a drug, prove it safe and effective through well-controlled clinical tests, and submit an NDA for FDA's approval. After the patent on this approved drug expires, some drugs still have a substantial market warranting continued manufacture and distribution. Drug firms other than the original firm may desire to market a drug comparable to one that was previously marketed.

FDA considers the current legislation as generally requiring the second drug firm to submit an NDA containing full reports of investigations that show the drug to be safe and effective. Thus, except for drugs for which FDA has determined that additional clinical trials are unnecessary, the second firm wanting to market the same drug must perform its own tests and submit full reports on the investigations to FDA. In turn, FDA reviewers must perform a comprehensive review of the NDA to assure that the reports show the drug is safe and effective for use as directed. According to the Secretary of HEW, the second firm's testing and FDA's review of the data waste both industry scientific resources and the time of FDA medical officers.

H.R. 4258 would require every drug firm to obtain a license from FDA before it could market a drug product (section 120). FDA could issue a drug product license only if (1) a monograph was in effect for the drug entity contained in that product and (2) the monograph provided for the dosage form and strength of that product (section 121(a)).

During the first 5 years after a monograph becomes effective, a second firm could be licensed only if (1) the original firm authorized FDA to issue the license or (2) the second firm submitted sufficient data and information which independently supported the issuance of a license (section 121(b)).

In effect, H.R. 4258 would give the original firm exclusive use of the data and information developed in support of the issuance of a monograph for 5 years. In the absence of any other patent-type protection, after the initial 5-year period, a second firm could obtain a license without the need for duplicate clinical tests.

FDA favors the provision because the exclusive use period provides the original firm with an opportunity to obtain a fair return on its investment. In addition, the provision will avoid duplicate industry testing for certain drugs.

S. 1075 would provide the original drug firm exclusive use of the data and information developed for 7 years. During this period, S. 1075 would require a second drug firm to go through the current FDA drug approval procedures. During the 7-year period, the drug firm could obtain the permission of the original firm to use the data submitted to FDA in support of the approval of the original drug. Beginning 7 years after the original drug was approved, another drug firm could submit an abbreviated application without the need for duplicate clinical tests. The application would be approved if the drug met appropriate standards, including identity, strength, quality, and purity (section 125).

These provisions in H.R. 4258 and S. 1075 would reduce the need for submitting to FDA clinical test data on marketed drugs--which represent about 50 percent of the NDAs submitted each year, as shown in the following table.

| <u>Year</u> | <u>Number of NDAs</u> | | <u>Percent</u> |
|---------------|-----------------------|---------------------------|----------------|
| | <u>Received</u> | <u>For marketed drugs</u> | |
| 1975 | 132 | 61 | 46 |
| 1976 | 127 | 69 | 54 |
| 1977 | 124 | 71 | 57 |
| 1978 | 121 | 57 | 47 |
| 1979 (note a) | <u>105</u> | <u>62</u> | 59 |
| Total | <u>609</u> | <u>320</u> | 53 |

a/Through August 31, 1979.

By reducing the need for submitting duplicate clinical studies, FDA should be able to more effectively use its limited number of reviewers.

REDUCING REGULATION IN THE EARLY PHASES OF NEW DRUG TESTING

Both proposals would reduce the impact of FDA on drug innovation, expedite the investigation process, and reduce FDA's regulation of the early phases of new drug testing.

Under the current system, a new drug that has promise for successfully treating human illness is first tested in animals. If the animal tests disclose no significant toxic effects and indicate probable therapeutic benefits, the manufacturer submits an IND to FDA for review. FDA exemption from the NDA approval requirements allows the manufacturer to conduct clinical tests using human subjects. Clinical tests are conducted in three phases--specifically, the new drug is administered to:

- A limited number of healthy persons and a few patients under carefully controlled circumstances by persons trained in pharmacology.
- A limited number of patients for a specific disease treatment or prevention.
- As many as 3,000 patients to assess the drug's safety and efficacy, and most desirable dosage under conditions that approximate how the drug would be prescribed and used once marketed.

In the first two phases, FDA regulatory emphasis concerns protecting human test subjects and evaluating whether the data obtained in the first two phases warrant expanding clinical tests on a larger population. Thus, manufacturers spend considerable research resources designing and demonstrating the quality and reliability of tests for these phases for all investigational drugs even though most of them never reach that stage of testing. Most investigational drugs do not go beyond the first two testing phases because they do not show enough therapeutic promise. FDA estimates that 90 percent of all INDs fall into this category.

The legislative proposals are designed to establish a comprehensive statutory restatement of the principles, policies, and practices with respect to the investigational stages of the drug approval process. These proposals should reduce any needless delay and unnecessary FDA regulation. As stated in Senate Report Number 96-321:

"The Committee believes that a number of major changes should be made in the way investigational drugs (i.e., unapproved drugs being tested for safety and effectiveness) are used. Many of these changes will expedite the drug investigation process, lowering the cost of drug research and development and permitting new drugs to be introduced earlier. Other changes are designed to provide clearer safeguards for participants in drug research and assure the accuracy and reliability of data."

H.R. 4258 would create the following three distinct categories of clinical investigations involving drugs that have not been approved by FDA (sections 125-133).

--Drug innovation investigations would consist of limited testing of drugs on small numbers of humans to assess their risks and effectiveness (section 127). FDA's regulatory review would be limited to aspects that may adversely affect the health or rights of the human participants.

--Drug development investigations would include more intensive testing of drugs on a larger number of humans to evaluate their effectiveness and risks (section 128). FDA's regulatory review and oversight during this type of investigation would be more expanded.

--Drug treatment investigations would allow the use of a drug on a small number of humans with a serious disease or condition who cannot be satisfactorily treated by other forms of therapy (section 129). The use of such drugs is intended to provide treatment rather than to assess risks or effectiveness.

The general objectives of these sections of H.R. 4258 are to protect the rights and health of humans who participate in clinical investigations and to avoid FDA's interfering with the discovery and development of new drugs. H.R. 4258 also provides for the establishment of procedures to ensure that clinical investigations are conducted as promptly as possible with as little FDA review and oversight as necessary while assuring proper protection of the public health.

S. 1075 would establish two categories of clinical investigations involving drugs that have not been approved by FDA. The first category, drug research investigations, would involve limited testing of drugs on small numbers of humans to assess the drugs' safety and effectiveness (section 126). The second category of compassionate or treatment drugs would allow drugs to be used on a small number of humans who have a serious disease or condition that has no adequate method of treatment (section 127).

Both FDA and the Pharmaceutical Manufacturers Association believe that these provisions will ease the burden on both FDA and the manufacturer. According to the FDA Commissioner, reducing the regulation during the investigational period should encourage more drug innovation in the United States. Most drug firms we visited stated that one reason drug research was increasing overseas was because they are less hampered by regulation there.

ACCELERATING APPROVAL OF BREAKTHROUGH DRUGS

Both legislative proposals would provide for provisional approval for the limited use of "breakthrough" drugs (major therapeutic advances) before adequate and well-controlled studies are completed demonstrating the effectiveness of the drugs. Under current legislation, FDA must disapprove an NDA if it finds that certain deficiencies exist with respect to the contended safety and effectiveness of the drug, including the lack of "substantial evidence" of the drug's effectiveness.

Under section 110 of H.R. 4258 and section 128 of S. 1075, the use of such drugs would be permitted on the market if certain conditions were met, including the following:

- The drug is intended for use in life-threatening or severe debilitating illness or injury.
- The drug constitutes a major therapeutic advance.
- Delaying its approval would pose significantly greater risks to patients than would immediate provisional approval.
- There is "significant evidence" of the drug's effectiveness rather than "substantial evidence" as previously required.
- Well-controlled tests are, if ethically and methodologically possible, underway.

A drug that meets these conditions would receive provisional approval for 3 years. This approval would be renewable if tests were still underway and all of the above conditions were met.

The need for complete testing to ensure that drugs meet the established standards of safety and efficacy has sometimes caused lengthy delays in the availability of drugs that represent major advances in treating serious illness. FDA believes the proposed authority for breakthrough drugs would accelerate the approval of drugs that are major therapeutic advances without opening a loophole for provisional approval of unsafe, ineffective, or unnecessary new drugs. Further, FDA believes this proposed authority would not compromise the safety of the drug since the Secretary of HEW will have to make a risk-benefit assessment similar to that made for all drugs before FDA approval. The Secretary will have less evidence of effectiveness, but the evidence will have to be sufficient to justify that the drug is safe (the benefits outweigh the risks) and offers major therapeutic advantages for patients with life-threatening or severely debilitating illness or injury.

The HEW Review Panel on New Drug Regulation--a group of prominent legal, medical, and academic persons established by the Secretary of HEW in 1975 to study FDA policy and procedures relating to the approval of new drugs--recommended that FDA be given statutory authority, in exceptional cases,

to release drugs on a limited basis before all testing is completed. The substance of sections 110 and 128 is consistent with the Panel's recommendation.

The Pharmaceutical Manufacturers Association believes both sections are too strict and inflexible. According to the Association, they set such "high hurdles" for breakthrough drugs that few drug firms would try to surmount them and even fewer would succeed. The Association believes that strictly mandating all the circumstances necessary to justify a provisional approval would not give the Secretary of HEW enough flexibility.

To establish the safety and efficacy of a drug, clinical studies take a long time--as much as several years--to complete. Provisional approval of breakthrough drugs would permit these drugs to be used much sooner than they become available under the current drug approval process.

The number of breakthrough drugs would most likely be small; therefore, the provision would have little impact on the total FDA review process. For example, of the 413 drugs FDA approved between January 1, 1974, and December 31, 1978, FDA estimated that only 7 (or 2 percent) would qualify as breakthrough drugs. The breakthrough provision could speed up the public availability of such drugs, whose use has been delayed by current standards. FDA advised us that the breakthrough provision is intended to apply to a small number of drugs that clearly represent major therapeutic advances on the basis of evidence that is less than the statutory standards. The significance of the provision is its benefit to patients from the early release of the drugs.

RESTRICTING DISTRIBUTION OF CERTAIN DRUGS

Section 108(e) of H.R. 4258 permits restricted distribution of certain drugs to a controlled environment but precludes general distribution because of the risk associated with them. For example, the drug may be used only under carefully controlled circumstances, such as in a hospital. Section 129(b) of S. 1075 contains similar provisions on restricted distribution.

Under current legislation, FDA cannot place any restrictions on either the drug's use or its distribution. The current law has been criticized because, while the risk from a drug may outweigh its benefits when the drug is considered

for general, unrestricted use, its benefits might clearly outweigh the risk if certain restrictions (e.g., hospital use only) were imposed so as to reduce the risk. Without authority to restrict distribution, drugs which may be of significant value when distributed and used in accordance with certain risk-reducing restrictions may be delayed in their marketing or may not be allowed to be marketed.

H.R. 4258 would give FDA the express authority to condition the approval of any drug on adherence to prescribed conditions relating to the distribution, dispensing, or administration of the drug. FDA could place such conditions on approved drugs only under certain circumstances:

- The risk of the drug product is so significant that the drug could not be determined safe unless the restrictions are imposed.
- The importance of such restrictions could reasonably be expected to reduce the identified risk sufficiently to permit such drug to be considered safe and effective.
- No other administrative or educational action could reasonably be expected to reduce such risk.

In addition, before FDA could place any conditions on the drug's distribution, the opinion of an advisory committee must be obtained. Also, FDA could not place any conditions on the use of a drug by experienced practitioners in certain facilities, such as hospitals, unless it determined that such conditions were necessary for the drug to be considered safe.

The American Pharmacist Association, the American Medical Association, and the Pharmaceutical Manufacturers Association all testified in 1978 congressional hearings against the language of the provision. The American Pharmacist Association believes restricted distribution of drugs violates the rights of pharmacists to dispense approved drugs without any Government official dictating which pharmacy may dispense a particular drug, regardless of whether or not the pharmacy is in a hospital. The Association further believes that patients could be discriminated against based on economics or geography because of the restricted distribution decisions.

The American Medical Association opposed a provision to restrict the distribution of drugs because it would transfer vital medical decisionmaking authority from the treating physician to FDA.

The Pharmaceutical Manufacturers Association testified that the provision's language is overdrawn and would be subject to misuse. Misuse could result in denying important new drugs to many licensed physicians and community pharmacists. This would further result in requiring their patients to go elsewhere for treatment at greater inconvenience and expense or to go without treatment. The Association believes that appropriate prescribing information to ensure that new agents are used suitably would be a prudent alternative to limited distribution authority.

Regarding restricted distribution of drugs in foreign countries and the United States, the FDA Commissioner, in June 1979 testimony before the House Subcommittee on Science, Research, and Technology, said that:

"In countries that have a system of national health insurance, such as the United Kingdom and Australia, it is possible to restrict reimbursement for certain drugs or to limit distribution of certain drugs to hospitals or to particular specialists. This permits the release of drugs with less evidence of safety or effectiveness, because the use of those products can be confined to the safest conditions or to those physicians who are most knowledgeable in their use. Additional data on safety and effectiveness may be gathered under these conditions. In the United States the law does not permit restricted distribution, and attempts by FDA to impose such restrictions have been defeated in the courts or have been dropped because of potential law suits. It is therefore important that adequate evidence be available at the time of marketing approval to provide a significant level of confidence that a drug is safe and effective for the patient population that will receive it."

Other medically sophisticated countries have restricted the distribution of certain drugs. This allows them to release the drugs with less evidence of safety and effectiveness because of the control inherent in the conditions under which the drugs were released and used. The patients' interests are protected because the use of these drugs is confined to the safest conditions or to those physicians who are most knowledgeable in their use.

POSTMARKETING SURVEILLANCE

Section 108(g) of H.R. 4258 and section 128 of S. 1075 generally would require drug manufacturers to establish and maintain a system for collecting and reporting adverse drug reaction information to FDA. Postmarketing surveillance is intended to monitor the use of a marketed drug to identify uncommon adverse reactions and to obtain more information on the incidence of reactions identified in clinical trials. Current legislation does not expressly require or provide for the establishment of systems for collecting and reporting by physicians, hospitals, or drug firms of information on the use of and experience with approved drugs.

These proposals would give FDA the authority to condition its approval of any drug with a requirement that the manufacturer oversee the use of and experience with the drug. This postmarketing surveillance requirement would be imposed where it is necessary or useful in evaluating the continuing safety of a drug. Under this requirement, the manufacturer would have to establish and maintain a system for identifying, collecting, and reporting data on the drug to FDA.

Improved postmarketing surveillance of drug use and experience is needed to provide information to determine whether further regulatory action should be taken with respect to an approved drug. When use of a drug by patients increases after approval, unexpected adverse effects may appear. A primary purpose of postmarketing surveillance is to identify those effects and assess their significance.

RESOLVING SCIENTIFIC DISAGREEMENTS

Section 133 of H.R. 4258 and section 126 of S. 1075 would provide informal procedures for resolving scientific disagreements during drug investigations. Current legislation does not provide for an informal means to resolve disagreements.

Both proposals would require FDA to establish informal and expeditious procedures for the review and, if possible, resolution of disagreements over the design or conduct of an investigation involving a drug. These procedures would give manufacturers an opportunity to confer with FDA on matters affecting their investigations without the necessity of resorting to formal proceedings. Further, both proposals would require greater use of expert advisory committees during drug investigations as well as the NDA approval process for

resolving disagreements. These proposals should provide a useful way for more promptly dealing with scientific disagreements.

FDA believes most disagreements are resolved quickly. Industry officials told us there was no established mechanism for promptly resolving these disagreements. Presently, drug firms can request administrative hearings to resolve such issues. This procedure is time consuming and seldom used. Industry officials did not provide specific examples of NDAs where such disagreements delayed the approval process, and we were unable to clearly identify such examples because of the technical nature of the issues discussed in correspondence between FDA and the industry.

AGENCY COMMENTS AND OUR EVALUATION

HEW indicated that proposed legislative reform concerning (1) abbreviated NDA procedures, (2) postmarketing surveillance, (3) breakthrough drugs, and (4) reduced regulation in the early phases of drug discovery should help speed up the drug approval process. Additionally, HEW believes that the proposed legislation to bring all classes of drugs under the same standard of regulatory control will also help speed up the process.

CHAPTER 6

USE OF COMPUTER SERVICES

FOR THE DRUG APPROVAL PROCESS

FDA reviewers did not extensively use available drug information systems in evaluating NDAs. This results, in part, from a lack of awareness of such systems and the reviewers' apparent reluctance to rely on automated information systems.

BUREAU'S USE OF COMPUTERS

The Bureau of Drugs obtains most of its data processing services from the Parklawn Computer Center. This center fulfills the automated data processing (ADP) needs of the Public Health Service and its constituent agencies (including FDA) by providing various ADP services, resources, technical support, and planning assistance.

The center reports administratively to the FDA Associate Commissioner for Management and Operations, but receives its financial support from the Public Health Service. It is functionally responsible to a user steering committee composed of senior level staff from each agency using the center. The center offers its services and facilities on a nonprofit, fee-for-service basis.

In addition to the Parklawn Computer Center facilities, the Bureau operates its own minicomputers which, according to FDA officials, can provide data transmission to the center. Bureau officials said a minicomputer located in the Bureau's Division of Information Systems Design is being used for data for several Bureau systems while the primary files are being maintained at the center. Some new small files will also be put on the minicomputer.

The statisticians in the Bureau's Division of Biometrics also use a minicomputer and have access to commercially available statistical programming software. The statisticians also do their own programming for analyses that cannot be handled by these commercial programs. Division of Biometrics officials said that the statisticians use computer assistance to analyze about 25 to 30 percent of the applications they review. The statisticians also have the option of requesting additional analysis or reformatting of drug data and may request that sponsors submit such data on punched

cards or magnetic tape. On occasion, they also ask the drug companies for the computer programs that were used to generate the data. Bureau officials said that they have the capability to make their own analysis of drug company data to corroborate the company's results.

The Bureau uses minicomputers in its laboratories to monitor and control data collection by laboratory equipment for use in quantitative analysis of drugs and to do repetitive calculations as needed.

REVIEWERS MAKE LIMITED USE OF EXISTING ADP SYSTEMS

According to Bureau of Drug officials, there are 17 computerized information systems within the Bureau. (See app. IV.) All of the systems, except for the Management Information System, contain drug-related information, and some of them may be useful to Bureau drug reviewers. However, reviewers' awareness and use of the information systems was generally limited.

We asked selected drug reviewers to identify the various information systems that they were aware of and could use in reviewing drug applications. Generally, they were aware of only 3 of the 16 systems:

- The ASTRO-4 drug information system: A system which contains historical and current information on INDs, NDAs, Form 5s and 6s, and abbreviated new drug applications. This system can be used to identify similar or related drug products, provide information in response to Freedom of Information Act requests, and produce publications.
- The management information system: A system to track the review of drug applications and related submissions.
- The adverse drug reaction reporting system: A system that contains current and historical reports of adverse reactions to marketed drugs as reported by drug manufacturers, hospitals, physicians, dentists, and others. Drug manufacturers holding NDAs are required by FDA regulations to report all adverse reaction information they become aware of. All other adverse reaction reports are submitted voluntarily.

Although not a "system," most reviewers also mentioned the Bureau's Medical Library as a source of information. According to FDA officials the Medical Library currently has access to over 150 unique data bases through four major systems, including those of the National Library of Medicine. These systems are used to provide a current awareness service designed to meet reviewers' interests. Users' profiles are maintained and listings of new references are automatically delivered to selected reviewers based on their profiles. Staff of the Medical Library includes specialists capable of performing extensive research tasks as well as literature searches.

Although reviewers were generally aware of the three systems, some did not know enough about them to be able to use them. Comments from reviewers regarding the Bureau's systems included:

- I've heard the term ASTRO-4, but I don't know what it is or what it contains.
- I've heard of ASTRO-4, but I depend on the consumer safety officer to get the data I need.
- I didn't know you could make specific requests of the adverse reaction reporting system.

One reviewer said that he was totally unfamiliar with the ASTRO-4 system and asked us to brief him on it. Another reviewer expressed little knowledge about information systems or what can be done with them. This reviewer was interested in being better informed about computer capabilities.

Almost all reviewers of drug applications we interviewed said they had never been briefed by the ADP department about available information systems and services or been given a user's manual 1/ for information retrieval.

Two reviewers recalled attending an ADP seminar several years ago. None, however, could recall attending any such seminars recently. One experienced consumer safety officer

1/A user's manual would include complete descriptions of what information systems are available within the Bureau and elsewhere, how to get the information, how long it might take, and whom to contact if problems arise in obtaining specific data.

told us that neither his division nor the Bureau had a training program dealing with ADP services or capabilities. One reviewer thought that a user's manual would be invaluable.

Even reviewers who were familiar with the three systems made little use of them in reviewing drug applications. During 1974 an FDA task force made three studies of the Bureau of Drugs' scientific information systems. Two of the studies, involving questionnaires, showed that chemists and consumer safety officers were the primary users of ASTRO-4. The third study, in which 203 search requests were analyzed, indicated that only about 20 percent of the requests applied to drug reviews. The Bureau concluded, from these studies, that pharmacologists, physicians, statisticians, and other scientific specialists were relatively low users of ASTRO-4.

We conducted a similar analysis of 350 ASTRO-4 search request forms submitted between July 1976 and July 1977 to determine how reviewers used this information system. The following table shows the results of this analysis.

| <u>Type of request</u> | <u>Number</u> |
|--|---------------|
| Freedom of information | 105 |
| Drug review | 32 |
| Chemical searches | <u>a/81</u> |
| Other (management, references, ADP, etc.) | <u>132</u> |
| | <u>350</u> |

a/This represented automated chemical searches, but we were not able to determine whether they had been used by a reviewer.

Regarding the Bureau's management information system, many of the reviewers we interviewed were aware of the system or had seen or used some of the reports it generates. Several reviewers, however, expressed concern that the system did not contain the types of information they thought it should. For example, one reviewer told us that a report that listed applications by drug trade name should also include the generic name. He said this would be an invaluable aid for drug review. When we explained, after checking with data processing personnel, that such information was available through ASTRO-4, he replied that it takes too long for that system to respond to requests and that the management information system provides more information and does not

require a special request. Most management information system reports are prepared on a regular schedule, whereas ASTRO-4 is request oriented.

FDA officials advised us that presently the capability of producing reports from multiple files has been provided, so that, if needed, a report from the management information system could be produced with generic information pulled from other files. Computer listings prepared on a regular schedule and computer output microfiche are available for all Bureau systems. Special requests for all systems, unless of an urgent nature, are held for up to 2 weeks, to hold down data processing costs.

While many of the reviewers were familiar with, and said they used, the adverse reaction reporting system, they expressed concern over the system's responsiveness and thought it incapable of providing information in an acceptable manner. However, rather than trying to change the system, or having tried and failed, reviewers appear willing to make do with what they have. FDA officials advised us that systems improvements are being implemented. FDA officials said also that other efforts are ongoing, through carefully monitored inpatient populations and through the use of survey data which estimates patient populations taking prescription drug products, to enable reasonable estimates of rates of occurrence to be developed.

Some reviewers noted that the adverse reaction reporting system does not indicate the statistical significance of the reaction because the reports are spontaneous and not associated with a known patient population. To determine statistical significance, the reviewer would have to know, as a minimum, the number of reactions and the total number of people who received that drug. Since these reports are for reactions to marketed drugs as reported by thousands of individual practitioners, it may be very difficult, if not impossible, to capture these data.

Other reviewers thought it less useful because the system is unable to identify a specific reaction. For example, a request for adverse reactions to specific drugs that caused cranial malformations in infants resulted in a compilation of data regarding congenital defects. This was as close as the system could come to answering this request. As a result, the reviewer had to wade through extraneous data to identify the needed information.

Other more technically oriented reviewers thought the adverse reaction reporting system should be overhauled; that it was too inflexible; and that it should be on-line, using direct access devices to respond to requests faster and more efficiently. FDA officials said that plans are being made to provide on-line access to subsets of the data base on the minicomputer to provide a capability for more rapid response and analysis. Reports are also run regularly and available on microfiche for rapid retrieval.

The Bureau's Division of Drug Experience, which maintains the adverse reaction reporting system, was modifying its operating procedures at the time of our review. In the past, the procedures for abstracting and preparing adverse reaction data for computer entry required screening by division reviewers, coding of data, keypunching by an outside contractor, and card input to the computer. The new procedures would eliminate the keypunching contract, transfer the coder/data input personnel to the division, and directly input data to the computer by remote terminals and a minicomputer. FDA officials told us that these new procedures are being implemented.

A Division of Drug Experience official believed that more could be done with computers in the adverse reaction area of drug surveillance. He cited management's lack of interest in past suggestions about ADP improvements as an impediment to a potentially more useful system. He also noted a lack of user-oriented service from the data processing office. FDA officials said extensive improvements to the system are being implemented which should make the system much more useful.

We analyzed 159 computer-assisted literature search requests to determine current library usage by review personnel. These requests were submitted to the library between July and December 1977. Our analysis showed that 37 requests (or 23 percent) were from drug review divisions. Of these, only 10 percent could be specifically attributed to the drug review process, with most requests coming from medical officers. These figures represent services for which we could identify a specific request document; they do not include, nor could we establish, the number of reviewers who used library services on a walk-in basis.

LACK OF USER INPUT TO SYSTEMS
DEVELOPMENT AND LACK OF
COORDINATION BETWEEN
USERS AND PROVIDERS

The needs of users of management and scientific information, which should be basic considerations of information systems design, appear to have received little consideration by Bureau system designers. Reviewers, generally, have not participated in the development of information systems.

The responsibility for developing, designing, and implementing the Bureau's automated information systems lies with the Division of Information Systems Design. With regard to systems development, a division official said the division attempts to respond to the needs of project managers but is hard pressed to do so with the current staff level. An ADP Users' Committee was established to monitor the adequacy of ADP services and to function as a sounding board for the needs of information system users. We were told, however, that the committee's work has been limited to reviewing ADP contracts for purchase or lease of ADP hardware and/or services. We requested minutes of committee meetings but were told that formal minutes were not maintained.

EXPERIMENTATION WITH MICROFICHE
SUBMISSIONS LACKS DIRECTION
AND APPEARS UNORGANIZED

In April 1973, a consulting firm hired to analyze the drug review process recommended that the Bureau consider using microfiche 1/ for reviewer referral to raw data contained in drug applications and for storage and retrieval.

Nearly 4 years later, in an address before a discussion group of the Academy of Pharmaceutical Sciences, the Bureau's Associate Director for New Drug Evaluation spoke of the ever-increasing bulk of drug applications and the need to do something about it. The address ended with an invitation to the drug industry "for volunteers for submittal of NDAs on microfiche." Shortly afterward, a microfiche NDA of purported excellent quality was submitted to the Bureau and assigned for review.

1/Microfiche is a sheet of photographic film, usually measuring 4 by 6 inches, capable of accommodating and preserving a considerable number of pages or documents in reduced form.

FDA officials told us that FDA has received and reviewed several microfiche submissions of clinical case reports. Guidelines for the submission of case reports on microfiche will be issued in the near future. Applicants will be strongly encouraged to provide data in this way. In some cases, hard copy case reports will also be required. This process has taken a considerable time due to the experimental nature of the effort and the need to review several submissions and involve a number of reviewers.

As to potential benefits, FDA officials told us that, if reviewers need to obtain information from an approved drug application that has been retired to the Federal Records Center, they may have to wait weeks or months for the center to act on the request. If the application were on microfiche, in a review division's document control room, it could be retrieved quickly, perhaps within minutes. Moreover, this easy access to approved applications may improve the drug review process as reviewers become comfortable with and learn of the ease with which application data can be obtained.

In addition, some savings may be realized through reduced storage space and handling costs associated with the present form of drug applications. For instance, it was estimated that, in fiscal year 1971, the Bureau received 20,069 submissions. Each of these was submitted in triplicate, resulting in a volume of over 6 million pages. The conversion of these documents to microfiche could reduce the storage requirements by more than 60 percent. 1/ Also, the cost of storing drug applications may be reduced by converting to microfilm or microfiche. For example, the cost of storing microfilm--one roll can hold up to 2,000 pages of printed information--is about 2 percent of the cost of storing an equivalent volume of paper. 2/ Similarly, one 4-by-6-inch sheet of microfiche can hold 270 pages of printed information.

Given the potential benefits of microfiche as a substitute for hard-copy drug submissions, we believe the Bureau should assess the potential of microfiche submissions.

1/Final report to FDA, Auerbach Associates, Inc., under contract No. FDA-72-63, April 15, 1973, pp. 2-1, 2-3.

2/Information Processing, Science Research Associates, Inc., 1976, Bohl, Marilyn, p. 77.

CONCLUSIONS

Drug reviewers in FDA's Bureau of Drugs rely greatly on the information contained in the drug applications they review to reach decisions regarding the safety and efficacy of proposed new drugs. Existing information systems did not appear to have been extensively used by the reviewers.

We believe Bureau management should evaluate the existing information systems to determine how well they serve the drug review process. A more concerted effort, such as training programs for drug reviewers, seems to be needed to enhance reviewer awareness and use of existing information systems. Also, the Bureau should make the systems more responsive to the needs of drug reviewers in order to increase use of the systems.

In the development of information systems, the needs of potential users--especially drug reviewers--have not been adequately considered. Some form of interface should be established to bridge the gap between drug reviewers, who have shown a historic reluctance to use automated information systems, and data processors to link the full capabilities of the technology with user needs.

More should be done to encourage the use of microfiche in the submission of supporting data for NDAs. Although this process is not critical to the drug review process, it could offer such advantages as quicker retrieval of data on related drugs, and monetary savings in storage and other associated costs.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the FDA Commissioner to evaluate the Bureau of Drugs information systems to determine how well they serve the drug review process. This effort should consider the need to:

- Increase the drug reviewers' awareness of existing information systems.
- Make the existing systems more responsive to the needs of drug reviewers by conducting more comprehensive surveys of the reviewers' needs.

- Encourage user participation in the development or redesign of information systems.
- Expedite the assessment of the potential benefits of using microfilm or microfiche submissions of new drug applications.

AGENCY COMMENTS
AND OUR EVALUATION

HEW concurred with our recommendation on evaluating the Bureau of Drugs' information systems to determine how well they serve the drug review process. HEW said steps will be taken to make appropriate information systems more accessible to the reviewers. According to HEW, many of the existing systems were designed to assist the management of the review process, or the handling of data for certain purposes, and were not intended to aid individual reviewers. HEW also said FDA will continue to evaluate the use of microfiche technology.

PROFILE OF ORIGINAL NDAs SUBMITTED IN 1975

| | <u>Number</u> | <u>Percent</u> |
|---|---------------|----------------|
| Total NDAs received | <u>132</u> | |
| Chemical type: | | |
| New molecular entity | 31 | 24 |
| New salt | 3 | 2 |
| New formulation | 29 | 22 |
| New combination | 3 | 2 |
| Already marketed drug (by another firm) | 61 | 46 |
| Already marketed drug (for new indication) | <u>5</u> | <u>4</u> |
| | <u>132</u> | <u>100</u> |
| Therapeutic importance: | | |
| Important therapeutic gain | 4 | 3 |
| Modest therapeutic gain | 17 | 13 |
| Little or no therapeutic gain | 109 | 83 |
| Less safe and effective than existing cures but has other advantages | <u>2</u> | <u>1</u> |
| | <u>132</u> | <u>100</u> |
| Reviewing divisions: | | |
| Cardio-renal drug products | 20 | 15 |
| Neuropharmaceutical drug products | 20 | 15 |
| Metabolism-endocrine drug products | 20 | 15 |
| Anti-infective drug products | 21 | 16 |
| Oncology and radiopharmaceutical drug products | 35 | 27 |
| Surgical-dental drug products | <u>16</u> | <u>12</u> |
| | <u>132</u> | <u>100</u> |
| Company size: | | |
| Large (research budget over \$30 million) | 25 | 19 |
| Medium (research budget \$10 million-\$30 million) | 26 | 20 |
| Small (research budget under \$10 million) | <u>81</u> | <u>61</u> |
| | <u>132</u> | <u>100</u> |

NUMBER OF MONTHS REQUIRED TO

APPROVE DRUGS BY COUNTRY

| <u>Drug</u> | <u>United States</u> | <u>Canada</u> | <u>Norway</u> | <u>Sweden</u> | <u>Switzerland</u> | <u>United Kingdom</u> |
|-----------------------------|----------------------|---------------|---------------|---------------|--------------------|-----------------------|
| Beclomethasone dipropionate | 26 | 8 | 8 | 19 | 7 | 5 |
| Sodium valproate | 5 | (a) | (b) | (a) | 45 | 3 |
| Cimetidine | 13 | 8 | 19 | 20 | 10 | 2 |
| Protirelin | 28 | (a) | (b) | 21 | 9 | (c) |
| Vidabrine | 23 | 12 | (b) | (c) | (c) | 6 |
| Somatotropin | 15 | (b) | (b) | 23 | 10 | 8 |
| Sodium iodide I-123 | 20 | (d) | | | | |
| Diazoxide | 40 | 11 | 14 | (a) | 14 | (c) |
| Phospho lipids | 14 | 24 | (b) | 43 | 3 | 7 |
| Amino acids | 12 | 16 | (b) | 23 | 7 | (c) |
| Danazol | 30 | 16 | 17 | 34 | 21 | 6 |
| Prazosin | 40 | 30 | 27 | (a) | 10 | 6 |
| Disophyramide phosphate | 54 | 19 | 36 | 80 | 17 | (c) |
| Propranolol: | | | | | | |
| Arrhythmias | 17 | 23 | 9 | 16 | 4 | 5 |
| Angina | 17 | 11 | 9 | 16 | 4 | 5 |
| Hypertension | 18 | 19 | 14 | 16 | 4 | (c) |

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a/Under review at agency at time of our review.

b/Not submitted to agency at time of our review.

c/Data not available.

d/Not available in other countries.

AVAILABILITY OF FOURTEEN
THERAPEUTICALLY IMPORTANT DRUGS
(earliest date underscored)

| | <u>Month and year available</u> | | | | |
|-----------------------------|---------------------------------|------------------|---------------|-----------------|--------------------|
| | <u>United States</u> | <u>Canada</u> | <u>Norway</u> | <u>Sweden</u> | <u>Switzerland</u> |
| Beclomethasone dipropionate | May 1976 | June 1976 | Nov. 1973 | Mar. 1974 | Nov. 1973 |
| Sodium valproate | Feb. 1978 | (a) | (b) | (a) | <u>May 1972</u> |
| Cimetidine | Aug. 1977 | May 1977 | July 1978 | June 1978 | <u>Sept. 1977</u> |
| Protirelin | Nov. 1976 | (a) | (b) | Dec. 1976 | Jan. 1977 |
| Vidabrine | Nov. 1976 | <u>Aug. 1976</u> | (b) | (c) | (c) |
| Somatotropin | July 1976 | (a) | (b) | <u>May 1971</u> | Apr. 1972 |
| Sodium iodide I-123 | Mar. 1976 | (d) | (b) | (c) | (c) |
| Diazoxide | May 1976 | <u>July 1969</u> | Dec. 1975 | (a) | Dec. 1973 |
| Phospho lipids | Oct. 1975 | <u>Oct. 1972</u> | (b) | Feb. 1964 | <u>Jan. 1963</u> |
| Amino acids | Dec. 1975 | May 1977 | (b) | Nov. 1972 | <u>Feb. 1966</u> |
| Danazol | June 1976 | Jan. 1976 | May 1978 | Oct. 1977 | <u>Apr. 1977</u> |
| Prazosin | June 1976 | Aug. 1976 | Sept. 1976 | (a) | June 1974 |
| Disopyramide phosphate | Aug. 1977 | Mar. 1977 | Aug. 1978 | May 1978 | Mar. 1977 |
| Propranolol: | | | | | |
| Arrhythmias | Nov. 1967 | July 1968 | Sept. 1966 | Nov. 1965 | Oct. 1965 |
| Angina | Nov. 1967 | June 1969 | Sept. 1966 | Nov. 1965 | Oct. 1965 |
| Hypertension | June 1976 | July 1974 | Aug. 1972 | Nov. 1965 | <u>Oct. 1965</u> |

a/Under review by agency at completion of our visit.

b/Not submitted to agency at completion of our visit.

c/Data not available.

d/NDA submission canceled.

BUREAU OF DRUGS INVENTORY OF
AUTOMATED INFORMATION SYSTEMS

| <u>System name</u> | <u>System objective</u> |
|---|--|
| ASTRO-4 Drug Information System | Maintains a file on INDs, NDAs, Form 5s and 6s, and abbreviated new drug applications. This system supports the review process, Freedom of Information Act request, and other reports. |
| New Drug Evaluation/ Management Information System | Maintains and tracks the status of INDs, NDAs, supplements, and amendments in management support of the review process. |
| Radioactive Drug Research Information System | Maintains and tracks the status of submissions by radioactive drug research committees in support of the review process. |
| Drug Product Defect Reporting System | Maintains a comprehensive file of drug product quality problems in support of the drug quality assurance program. |
| Bioresearch Monitoring Information System | Maintains a comprehensive file of clinical and nonclinical facilities and clinical investigators in support of the bioresearch monitoring program and the review process. |
| Biopharmaceutic Review Management Information Antibiotic System | Maintains information pertaining to INDs, NDAs, abbreviated new drug applications, and Form 5s and 6s which are undergoing or have completed biopharmaceutic review. |
| OTC Management Information System | Maintains information from submissions, comments, and correspondence and tracks the status of various documents in support of the review of over-the-counter drugs. |

| <u>System name</u> | <u>System objective</u> |
|---|---|
| Compliance Management Information System | Provides a tracking capability for regulatory actions in support of the drug quality assurance program. |
| Drug Experience Information System | Maintains files of adverse effects to marketed drugs in support of postmarketing surveillance activities and the review process. |
| Drug Efficacy Study Implementation System | Maintains data on drug products reviewed by the National Academy of Sciences as a result of the 1962 Amendments to the FD&C Act. Provides reports reflecting the status of drugs undergoing this review. |
| Drug Abuse Treatment Monitoring System | Maintains information on the use of methadone and other treatment modalities in drug abuse treatment programs. This system is used to monitor program performance. |
| Antibiotic Batch Certification System | Aids in laboratory management of the antibiotic certification process, expedites the process, and provides an automated billing capability. Historical information maintained is used for review of testing procedures. |
| Drug Regulation and Listing System | Maintains data files of drug establishments and drug products listed under the Drug Listing Act of 1972. Supports the drug quality assurance program, Freedom of Information Act requests, and the publication of the National Drug Code Directory. |
| Management Information Resources System | Provides administrative support to Bureau programs through maintenance of a personnel inventory and history of personnel actions. |

| <u>System name</u> | <u>System objective</u> |
|---|--|
| Poison Control System | Maintains data files on poisonings in support of the poison control program. |
| Abbreviated New Drug Application Management Information System | Maintains and tracks the status of abbreviated new drug applications in support of the review process. |
| Biometrics | The Division of Biometrics provides statistical design and analysis support to the review process and other Bureau programs. This Division uses standard statistical computer programs and develops additional programs as required. |
| Automated Nationwide Acquisition of Laboratory Information System | Contains information collected nationwide on laboratory assay results of drug products in support of the drug quality assurance program. |
| Laboratory Automation System | A variety of automated and semi-automated laboratory instruments support the regulatory and testing functions of Bureau laboratories. |
| Word Processing | Microprocessor based, shared logic word processing systems are now used throughout the Bureau and are currently being installed in all review divisions to provide more effective and efficient typing support. |
| Medical Library | Four computerized search service systems providing access to over 150 unique data bases, includes domestic and foreign drugs. |



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

APR 7 1980

OFFICE OF THE INSPECTOR GENERAL

REFER TO:

Mr. Gregory J. Ahart
Director, Human Resources
Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Food And Drug Administration's Drug Approval Process Takes A Long Time." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard B. Lowe III
Acting Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
ON THE COMPTROLLER GENERAL'S REPORT ENTITLED, "FOOD AND DRUG
ADMINISTRATION'S DRUG APPROVAL PROCESS TAKES A LONG TIME"

The Department of Health, Education and Welfare is aware that the evaluation of new drugs in the United States takes considerable time. The process is lengthy for some valid reasons: the system is deliberate and thorough; it operates on the basis of an administrative record which contains the evaluations of the data and evidence submitted by applicants. Once a drug is approved in the U.S. it may be marketed to more than 200 million people—the single largest drug market in the developed world. Approval by FDA also opens the door to approval in many other countries which respect the quality of FDA's evaluations and follow its lead.

Although the Department is satisfied that its evaluation process is of the highest quality, we continue to seek ways to improve its timeliness and responsiveness. We recognize that drug evaluation carries with it the dual responsibility to assure protection of the public from drugs which are unsafe or ineffective while simultaneously assuring that new drugs which offer therapeutic gains over currently marketed drugs are identified and brought to the market as expeditiously as possible. To achieve the latter aim, we have given extensive attention to the policies, procedures, and management of the evaluation process. We have implemented a number of initiatives to streamline and improve its management. Among the most important ones are:

- o Establishing goals under the Department's Management Initiative Tracking System (MITS) and Operational Management System (OMS) to reduce, over a three year period, FDA processing time on new drug applications by:

25% for drugs that represent important or modest therapeutic gains, and 15% for all other drugs.

At this time, FDA is on schedule in meeting these goals.

- o Establishing conditions for the acceptance of data from foreign clinical studies in support of NDA's.
- o Initiating a major revision of the IND/NDA regulations to streamline the review process and to eliminate any out-moded or unnecessary requirements to approval.

- o Implementing a Drug Classification System to aid in identifying those drugs with potential for therapeutic gain and to afford those drugs a priority review.

The Secretary has initiated a review of the current system in an effort to assist the FDA in looking for ways to expedite the drug approval process. All possible avenues for improvement will be explored. In addition, the Department has sought sponsored statutory reform in the Drug Regulation Reform Acts of 1978 and 1979. Important provisions in that legislation include:

- o Bring all classes of drugs under the same standard of regulatory control, thus ending the distinctions which are the result of a legislation patchwork, some over 40 years old.
- o Make legal by statute the Abbreviated NDA (ANDA) procedure to reduce the burden of unnecessary clinical testing to approve generic versions of already approved drugs, thus expediting the access to generic drugs.
- o Provide authority to FDA to require manufacturers to conduct postmarketing studies of their drugs to define certain adverse effects or risks in particular conditions or population groups, and to develop evidence of effectiveness of use in new indications to update labeling.
- o Provide authority to permit easy marketing of drugs which are clearly major therapeutic breakthroughs under a procedure which would assure that the complete evidence for final approval based upon the required standard for efficacy is collected.
- o Remove unsafe drugs from the market more quickly.
- o Reduce regulation in the early phases of drug discovery.

While the report discloses that drug evaluation is a lengthy process, it does not provide evidence of inordinate delays. In its comparisons between the processes of the U.S. and several European countries only testimonial reports of interviews with foreign drug industry representatives and the opinions of one or two foreign drug regulatory officials are reported. There is no comprehensive analysis or comparison of drug evaluation or approval processes between the U.S. and any of the foreign countries. There is no description or discussion of differences in benefit-risk analyses.

The lack of comparable data, the absence of a bias free sample, and the absence of rigorous analysis in Chapter Two of the GAO report preclude a valid or reliable conclusion about the comparability of approval time in the countries. Based on the evidence and arguments in the GAO report both of the following statements are true: Some important drugs are approved earlier in the U.S.; some important drugs are approved earlier in foreign countries. GAO makes only the latter statement.

Our major comments are as follows:

1. Any policy critique of the U.S. drug regulatory system must be sensitive to the need to strike an appropriate balance between the adequate scientific testing of new drugs, the therapeutic needs of patients, and the property rights of drug manufacturers. Any suggestion for revision should consider improving the system as a whole, not just one area to the detriment of the whole. The narrow focus of this Report on speed of approval alone is unbalanced. Neither the feasibility of speeding up the process with current resources nor the health risks of adopting a quicker, more superficial review process is considered in this Report.
2. The fundamental point emphasized by the Report, beginning with the title, is that drug approvals take a long time. While acknowledging that relatively few decisions on new drug applications are made within the statutory time frame of 180 days, we wish to emphasize that the law does not require a drug to be approved in six months. Rather, it explicitly provides that the parties may agree to a longer period. The majority of applications are not approvable on original submission; evidence of safety, effectiveness, or manufacturing and controls processes are inadequate to satisfy applicable legal and scientific standards. In these circumstances, FDA has opted to send manufacturers "non-approvable (action) letters," which outline the deficiencies in the application and indicate what additional information the manufacturer must submit in order to obtain approval.

Moreover, pursuant to 21 CFR S. 314.6, submission of significant additional information by a firm following receipt of a non-approvable letter starts anew the statutory time for review. Thus, because many new drugs cycle one or more times back to the manufacturer before being approved, the total time legally permitted for review becomes, in undecided situations, well more than 180 days. A factually accurate analysis would require that review cycles be measured against the 180 day time limit, rather than the total time from initial submission to final approval. GAO examined the number of review cycles which all NDA's submitted in calendar

year 1975 have gone through before approval or until the present time. The report does not describe the results of this analysis against the provisions of S. 314.6.

3. A fact that GAO does not include in its report is that some drugs are approved first in the U.S. The report expresses a bias that first is best, i.e., the country to first approve a new drug for marketing is at a competitive health advantage to other countries which approve the drug later. Each new drug tends to be marketed first in the country where it is developed. The scientific capacity to develop new drugs is distributed widely throughout the developed world. Thus, any drug developed outside the United States is likely to appear first in that country. Those drugs developed in the U.S. are also likely to be marketed first in the United States. Of all new molecular entities introduced into world medicine in the past decade, no single country has approved more than 50% of the total. The few important drugs that genuinely advance medical care, however, tend to be approved today at reasonably similar times (generally within a few months) in most developed countries of the world.

The isolated examples cited of drugs available in Europe but not in the U.S. are not evidence of anything except the known phenomenon that different countries often have different drugs. Moreover, the report does not identify the criteria for selecting the drugs upon which the international comparisons were made. The sample is biased in favor of drugs approved in other countries before they were approved in the U.S. No attempt was made to examine a sample of drugs approved in the U.S. before they were approved in any of the other countries studied. No conclusions about differences in benefit-risk analyses are possible.

4. All previous Congressional oversight of the agency, including the many hearings held by the House Intergovernmental Operations Subcommittee (L. H. Fountain, Chairman) and the Senate Subcommittee on Health and Scientific Research (Senator Edward M. Kennedy, Chairman) has emphasized the importance of this relationship between a regulatory agency and the regulated industry. The DHEW Review Panel on New Drug Regulation (Dorsen Panel), dealt extensively with this issue and again emphasized the importance of the general relationship that now exists between FDA and the industry. We believe this Report is biased in a direction that is out of context with these several previous oversight and review bodies or even with expressed caution and criticism set forth in several previous GAO reports.

GAO, itself, in previous reports¹ on FDA compliance with applicable conflict-of-interest statutes and regulations, has cautioned the agency against the use of consultants with interests in the regulated industry unless their interest is not so substantial as to affect the integrity of their services. Persons whose interests exceed the agency's guidelines for waiver under this provision are presently barred from advising the government on matters relating to drug regulation unless a waiver in accordance with 18 USC 208(b)(1) is granted. We believe the previous GAO position regarding special government employees reviewing drugs is appropriate and in line with current national policy.

The objectivity of FDA decisions and the public credibility of the regulatory process both depend in part on our sensitivity to and enforcement of the conflict-of-interest laws. Although this does inhibit to some extent the appointment of certain experts to advisory committees, this result was intended by Congress, and the problem is not a critical deterrent to recruiting good scientists to these advisory committees.

5. The Report asserts a serious misconception about the confidentiality of adverse reaction reports sent to the FDA. Contrary to the view repeatedly stated in the Report, adverse reaction reports sent to the FDA are maintained in the most confidential manner as required by the Privacy Act. Although summary data are available under the Freedom of Information Act, material sent to the public contains no identifying information. Some two thousand reports of adverse reactions are submitted voluntarily to FDA each year and physicians frequently provide additional information about incidents

¹ The relevant GAO reports are:

"The Food and Drug Administration's Financial Disclosure System for Special Government Employees: Progress and Problems." January, 1977.

"Financial Disclosure System for Employees of the Food and Drug Administration Needs Tightening." January, 1976.

"Need to Establish Safety and Effectiveness of Antibiotics Used in Animal Feeds." June, 1977.

"Answers to Questions on the Regulation of Biological Products." (in preparation).

of adverse reactions to drugs upon request from FDA. We believe this attitude and response attests to the confidence placed in FDA's ability to protect the identity of all persons or institutions connected with reported adverse drug reactions. FDA is aware of no instance where patient or physician confidentiality related to an adverse reaction report has been violated as a result of the Freedom of Information Act. Because the repetition of this error in a GAO Report could seriously undermine physician cooperation in reporting adverse reactions, it is essential that this section of the Report be corrected.

GAO Recommendation

We recommend that the Secretary direct the Commissioner of FDA to:

- Monitor the effect of FDA's actions to achieve the 25% and 15% goals over the 3-year period and revise its actions when necessary to assure that these goals are met.

HEW Comment

We concur. Two years ago the Secretary established these goals and instructed the Commissioner to give them a high priority within the agency. One of the objectives reported to the Secretary under the management tracking system. Periodic reports of progress are required and corrective action is taken whenever necessary to assure that this goal is met. FDA is currently on schedule to meet these goals.

GAO Recommendation

- Establish additional goals until the statutory 6-month time period is achieved or propose to the Congress that it revise the statutory 6-month timeframe.

HEW Comment

We have elected the second option. The Administration has already asked Congress to extend the statutory period for new drug approval from 6 months to one year in the Drug Regulatory Reform Legislation (H.R. 4258).

GAO Recommendation

- Use paraprofessionals to assist reviewers, particularly the reviewers with heavy workloads.

HEW Comment

We are currently considering the use of paraprofessionals to assist reviewers. We have initiated a feasibility study to determine the usefulness of paraprofessionals. Six technicians are currently being trained to assist reviewers. These results will be evaluated before beginning broader training and use of paraprofessionals.

GAO Recommendation

- Minimize involvement of reviewers in special projects.

HEW Comment

We do not concur. The role of reviewers should not be limited to analysis of NDA's. The "special projects" identified by GAO are an integral part of the overall drug review process. For example, reviewers are responsible for evaluating investigational new drug exemptions and supplemental new drug applications, handling safety problems with approved drugs when they occur, preparing guidelines for the clinical evaluation of specific drugs alone, manufacturing and controls guidelines, establishing labeling for drug classes and specific drugs, advising drug firms on protocols to study non-prescription drugs, contributing to the DESI review, meeting with scientific advisory committees, industry or other groups, and responding to Congressional and other priority correspondence. Through involvement in these activities, reviewers are able to assure consistency and continuity of the agency's activities.

GAO Recommendation

- Provide industry with timely feedback on deficiencies in NDAs and instances where industry is responsible for delaying approval of new drugs.

HEW Comment

We agree in the principle of feedback. FDA currently provides industry with feedback on deficiencies in NDAs during the review process through

deficiency letters as well as a full response when the review is completed. In addition, the agency is revising the investigational new drugs and NDA regulations to make their responses to applications more timely.

When an applicant is responsible for delaying approval of a drug, FDA has no legal authority and little leverage to force the applicant to correct the application. If a manufacturer has made a decision not to complete an application because of its competing priorities, then FDA should not interfere.

GAO Recommendation

- Expedite development of an improved post-marketing surveillance program, and provide for feedback on the results of the program to reporting physicians.

HEW Comment

We concur. Considerable progress has already been made toward implementing this recommendation. Since 1977 FDA has been engaged in a joint venture with the National Bureau of Standards Center for Field Services to determine the best method for identifying adverse effects of new drugs within the first five years following approval.

FDA has made considerable progress and improvements in its post-marketing surveillance system in recent years. The recent report of the Joint Commission on Prescription Drug Use describes in detail the comprehensiveness of the U.S. system.

FDA has established registries of eye and liver reactions to drugs, increased its activities to collect information about drug reactions through the Boston Collaborative Drug Surveillance Program, a program which is designed to estimate the rate of drug reactions as well as their nature and severity and supports other intensive surveillance and event monitoring systems through extramural contracts. This information derived from these sources is essential in assessing the risks associated with drugs and in determining whether the risks outweigh the benefits. Other recent efforts include: (1) monitoring medical literature and publishing alerts of adverse drug effects; (2) analysis and publication of drug use trends; and (3) increased intramural activity to gather and disseminate information about adverse drug reactions. An example which shows the capability of the post-marketing surveillance system in the U.S. was the recent removal of ticrynafen from the market for liver toxicity six months after it was introduced. This reaction

had not been flagged in France after 2 years of being marketed. The United States is unique among major drug regulatory countries for its legal requirement that drug firms report promptly adverse reactions to the FDA.

Health professionals who report adverse drug reactions are given feedback in the form of a letter and a computer printout of other reactions reported on the same drug.

GAO Recommendation

- Require that the FDA formally clarify its policy on the acceptance of foreign data.

HEW Comment

We concur. FDA published a regulation in April 1975 (set forth at 21 CFR 312.20) establishing the basis upon which foreign data may be submitted in support of a new drug application. Because GAO has expressed belief that there is confusion within the industry on this issue, FDA will issue a statement to clarify its policy of the acceptability of foreign data.

GAO Recommendation

We recommend that the Secretary direct the FDA Commissioner to evaluate the Bureau of Drugs information systems to determine how well they serve the drug review process. This effort should consider the need to:

- Increase the awareness of drug reviewers to existing information systems.
- Make the existing systems more responsive to the needs of drug reviewers by conducting more comprehensive surveys of the reviewers' needs.
- Encourage user participation in the development or redesign of information systems.
- Expedite the assessment of the potential benefits of using microfilm or microfiche submissions of new drug applications.

HEW Comment

We concur. We will take steps to make appropriate information systems more accessible to the reviewers. Many of the existing systems were designed to assist the management of the review process or the handling of data for certain purposes, and were not intended to aid individual reviewers. FDA will continue to evaluate the use of microfiche technology.

GAO Recommendation to the Congress

We recommend that the Congress consider:

- Modifying the FD&C Act to protect the confidentiality of drug experience reports submitted to FDA by physicians, hospitals and others.

HEW Comment

We do not concur. The Report is in error in stating that the identity of patients, reporting physicians, hospitals, or clinics is currently disclosable under the Freedom of Information Act. FDA does not reveal such information, and repetition of this misconception in this Report could impede the agency's efforts to obtain voluntary reports of adverse drug reactions.

GAO Recommendation to the Congress

- Establishing by law a committee which would have the responsibility to review and approve or recommend approval of all important new drugs. Consideration might also be given to authorizing experts who have a vested or financial interest in a drug firm to be appointed as a non-voting member of the committee.

HEW Comment

We do not concur. There are basic differences in the philosophy and style of government between the United States and other countries of the world that employ expert committees to judge which drugs may be marketed and which may not. Such a system offers no advantage in the U.S. over the present system and presents several disadvantages.

In the U.S. three factors make the situation different than in other countries: (1) regulatory decisionmaking is conducted in the open on the basis of documented evidence and with proper procedural protections for the rights of all parties; (2) petitioners before the government have the right to sue the government to resolve differences of opinion between the petitioner and the government; (3) public Congressional oversight over government programs is common. These basic factors would prevail in this country and influence the drug approval process even if a single prestigious committee were established to review and approve drugs. Thus, we do not believe this recommendation would speed up the drug approval process.

Currently, FDA employs 13 scientific advisory committees composed of experts in the medical specialties by which the drugs of particular classes are used, clinical pharmacologists, and biometricians as epidemiologists. The agency is in the process of appointing consumer endorsed nominees to the committees as full voting members. The committees assist FDA in evaluating the safety and efficacy of new drugs and advise the agency on whether certain drugs are supported by substantial evidence of effectiveness. The agency considers the committees' advice in its decisionmaking.

We do not concur with the GAO proposal that consideration be given to authorizing experts with vested or financial interests to serve on the suggested major committees proposed or FDA's current advisory committees. See discussion under Point 4 of the General Comments.

GAO Recommendation to Congress

- Giving FDA authority to restrict the distribution of new drugs so that they could only be used, for example, by certain specialists, or administered only in a hospital setting. Provisions for such authority are included in pending legislation.

HEW Comment

We concur. This recommendation is included in legislation proposed by the Administration (Drug Regulation Reform Act of 1979).

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