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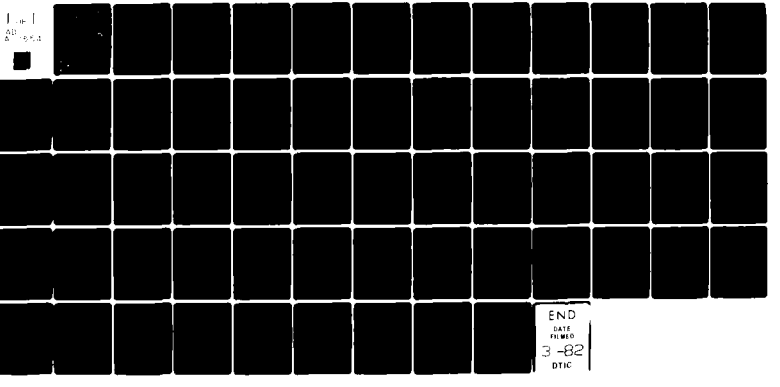

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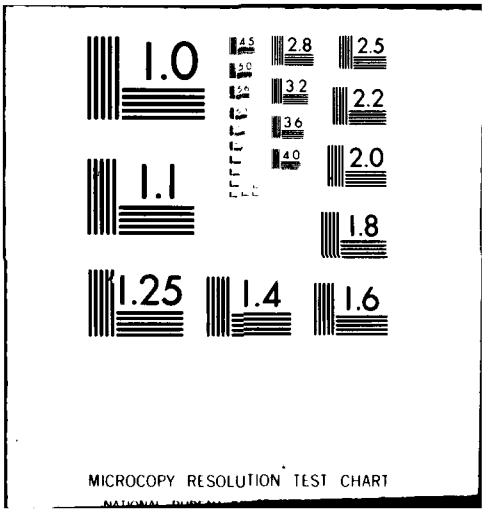
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REPORT BY THE

Comptroller General

OF THE UNITED STATES

Speeding Up The Drug Review Process: Results Encouraging -- But Progress Slow

The Food and Drug Administration's efforts to speed drug review are encouraging. Since October 1, 1978, FDA has approved more drugs in less time than before despite an increased workload. The greatest reductions were made in approvals of important drugs (drugs that in FDA's judgment provide a therapeutic gain over any marketed drugs). However, these approvals represent only about 41 percent of those in process since October 1, 1978, and it is too early to tell whether the positive trend will continue. Reduction of approval time has not been consistent throughout all FDA divisions, and processing times should be further reduced.

GAO is recommending actions that the Secretary of Health and Human Services could take to further reduce drug review time.

HRD-82-16

NOVEMBER 23, 1981

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

B-205294

The Honorable James H. Scheuer
Chairman, Subcommittee on Natural Resources,
Agriculture Research, and Environment
Committee on Science and Technology
House of Representatives

Dear Mr. Chairman:

At your request, we have reviewed the Food and Drug Administration's (FDA's) drug review process to determine the status and effectiveness of FDA's efforts to reduce the processing time of new drug applications.

As discussed with your office, we concentrated our efforts on three areas: (1) recent new drug application approval data to determine whether FDA was making progress in speeding up the process, (2) a number of recent FDA initiatives aimed at speeding up the drug review process to determine the status of their implementation, and (3) other suggestions that have been made to speed up the drug review process and determine the extent to which they might be implemented by FDA.

The report includes recommendations to the Secretary of Health and Human Services. FDA provided written comments on our draft report. (See app. I.)

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 congressional committees interested in FDA's drug review process; the Secretary of Health and Human Services; and the Director, Office of Management and Budget.

Sincerely yours,

Charles A. Bowsher

Comptroller General
of the United States

COMPTROLLER GENERAL'S REPORT TO THE CHAIRMAN, SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT, HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

SPEEDING UP THE DRUG REVIEW PROCESS: RESULTS ENCOURAGING--BUT PROGRESS SLOW

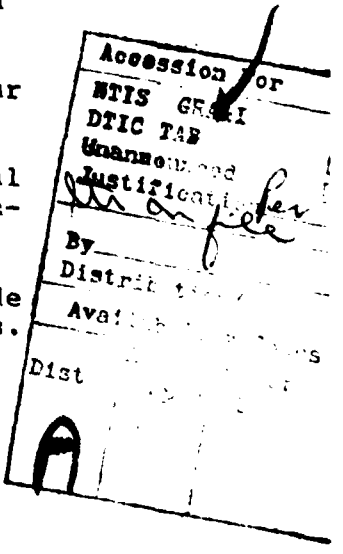
D I G E S T

At the request of the Chairman, Subcommittee on Natural Resources, Agriculture Research and Environment, House Committee on Science and Technology, GAO reviewed the Food and Drug Administration's (FDA's) efforts to speed up the drug review process. GAO compared the time required to approve new drug applications received by FDA during fiscal years 1976 and 1977 with the time required to approve those received in fiscal years 1979 and 1980.

REVIEW TIME PROGRESS NOT CONSISTENT

FDA has made some progress in reducing processing time for new drug applications, particularly for important new drugs. GAO's review showed that applications for the approval of important new drugs received in fiscal years 1979 and 1980, which had been approved as of July 1981, were processed in an average time of 10.0 months, or 5.7 months (36 percent) faster than similar applications received in fiscal years 1976 and 1977, which had been approved as of July 1978. Progress among FDA's six reviewing divisions, however, has not been consistent; in fact, four divisions have increased review time.

While FDA's progress is encouraging, additional time and analyses of larger numbers of applications are required to more accurately measure FDA's improvement. FDA also needs to improve the reliability of its computer data to provide an accurate basis for monitoring this progress. (See p. 8.)



FDA INITIATIVES TO EXPEDITE DRUG REVIEW PRODUCING MIXED RESULTS

FDA has undertaken a number of initiatives designed to speed up the drug review process, but these initiatives produced mixed results. Conferences between FDA and industry officials at the end of phase II clinical testing were enthusiastically supported by most industry representatives with whom GAO spoke. (See p. 12.)

FDA's effort to speed the review of chemistry data by having firms submit this information for drugs classified as major or modest therapeutic advances before submitting the full new drug application can help expedite review, but firms rarely do this. Only 6 of the 37 eligible firms have submitted these data early since this policy was implemented in December 1978. In some cases, the information submitted helped the chemist to complete the review in a timely manner. In others, however, the firm substantially changed the data when the full application was submitted. This required the chemist to duplicate much of the review. (See p. 13.)

FDA's requirements for giving priority review to important new drug applications have not been communicated in writing. Many reviewers have not understood FDA's priority review and therefore some treat important drugs no differently from other drugs. (See p. 14.)

Others attempt to expedite processing by more closely communicating with the drug sponsor or requesting earlier laboratory validation of analytical methods.

Validation of the methods used by the sponsor to insure the quality, strength, purity, and identity of a drug continue to take much longer than FDA's 45-day goal despite FDA's efforts to speed up the process. Many delays result from a lack of clear agreement among chemists as to what validations should involve and what type of data FDA laboratories need. Delays also result from errors or omissions in samples and data submitted by sponsors. (See p. 17.)

Additional efforts are needed to speed up the work of the Division of Biometrics, which examines the statistical data in the new drug application, and the Division of Biopharmaceutics, which reviews studies of such things as the drug's rate of dissolution in the blood. These divisions' data requirements are not being adequately communicated to new drug application sponsors. Also, reviewers in some FDA divisions wait until they are well into their review before identifying the material to be reviewed by these divisions. (See p. 20.)

REWRITE OF DRUG APPROVAL REGULATIONS SLOW

As early as March 1978 the Commissioner of FDA expressed the agency's intention to rewrite its regulations on investigational new drugs and new drug applications. As of August 1981, a draft of the regulations had not been released for public comment. FDA has stated that a draft of the revised new drug application regulations will not be available for public comments before March 1982 and that these regulations will probably not be final for at least 2 more years. A draft of the revised investigational new drug regulations is not expected to be available for comments until October 1982. (See p. 26.)

To determine the types of changes likely to be made in the drug review process, GAO interviewed cognizant FDA officials in the Bureau of Drugs to obtain their reactions to some suggestions for speeding up the drug review process that have been made by various organizations and individuals. These interviews indicate that FDA will make some changes that should help improve the efficiency of the drug review process. Other suggested changes have apparently been considered and not entirely accepted. According to the Associate Director for New Drug Evaluation, none of the changes being considered will revolutionize the drug review process, nor are they expected to cause a dramatic decrease in the time required for new drug review.

FDA expects that proposed regulation revisions will cut several months to a year or more off the average 7-year period from the beginning of human testing to approval of a new drug for marketing. The Commissioner of FDA will be evaluating the drug review process to determine whether additional managerial improvements could improve the overall review and regulation of drugs. (See p. 26.)

This report summarizes many suggested changes for speeding up the drug review process made by the Pharmaceutical Manufacturers Association, representatives from industry, and former FDA regulators. It also discusses the actions FDA officials believe will be taken on each. (See p. 27.)

CONCLUSIONS

GAO believes FDA should revise its system for measuring its progress in reducing drug review time. The system should compare approval rates on new drug applications submitted to FDA during comparable periods of time before and after initiation of FDA actions to speed up the drug review process. Before revising the system, however, FDA must develop an accurate, computerized data base from which to work. With easy and timely access to accurate information, FDA managers can quantitatively analyze their progress from a historical perspective for the agency as a whole and for each operating division. In doing so, they can determine the progress being made to achieve their goals and objectives. (See pp. 8 and 9.)

GAO believes that FDA's initiatives to speed up specific tasks associated with the drug review process are a step in the right direction although they have produced only limited results to date. Greater use of end-of-phase-II conferences, the establishment of a meaningful priority review system, speeding up methods validation and the work of the Divisions of Biometrics and Biopharmaceutics, and the earlier submission and review of chemistry data should help to improve the efficiency of FDA's drug review system and reduce review time. (See pp. 22 and 23.)

It is difficult to determine the extent to which the changes FDA is considering will speed up the drug review process. Many of the changes are procedural. The extent to which they will improve communication between industry and FDA is unknown and can only be assessed over time. (See p. 36.)

RECOMMENDATIONS TO THE SECRETARY OF HEALTH AND HUMAN SERVICES

The Secretary should direct the Commissioner of FDA to:

--Revise its system used in measuring FDA's progress to provide for the types of comparisons identified in this report.

--Develop an accurate computerized data base on which such a system would draw by correcting the errors in the existing computerized data base.

--Publish annually quantitative data showing approval rates for each type of drug (new molecular entities, new salts, new formulations, etc.) by each reviewing division, for use by program officials and the Congress. (See p. 9.)

For further recommendations on specific actions FDA could take to speed up the drug review process, see pp. 23, 24, and 38.

The Secretary should also direct the Commissioner of FDA to prepare a report to the Chairman, Subcommittee on Natural Resources, Agriculture Research and Environment, House Committee on Science and Technology, detailing each change it has made or will make to speed up the drug review process and estimating the amount of review time the change has saved or is expected to save. The report should address each of the suggestions for speeding up the drug review process discussed in chapter 4 of this report, along with any others FDA considers important, and indicate the extent to which its rewrite of the new drug regulations

will address each and, in cases where it disagrees, the specific reasons for disagreement. (See p. 38.)

The report should also contain information on the extent to which (1) individual reviewers are accepting or rejecting foreign data submitted in support of new drug applications and (2) additional domestic verification is required. The report should be issued by June 30, 1982. (See p. 38.)

AGENCY COMMENTS

The Department of Health and Human Services (HHS) stated that it appreciated GAO's recognition of FDA's progress and agreed that there are inconsistencies in performance across the six FDA reviewing divisions and that further opportunities are available to reduce drug review time. HHS agreed with most of GAO's recommendations and stated that FDA's Commissioner has recently appointed a task force to examine the drug approval process and report to him on their recommendations for improvement. According to HHS, the task force, which includes members of FDA and other components of the Department, will go beyond past efforts and fully consider wide-ranging matters. HHS stated that it shares FDA's concern and will be consulted throughout this process.

HHS cautioned that the comments made in response to GAO's recommendations are subject to reconsideration as the Commissioner, his task force, and HHS give this matter the scrutiny it deserves. HHS comments are discussed on pages 9, 24, and 38 and are included as appendix I to this report. (See p. 46.)

Contents

ABBREVIATIONS

ANDA	abbreviated new drug application
CSO	consumer safety officer
DESI	Drug Efficacy Study Implementation
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GAO	General Accounting Office
HHS	Department of Health and Human Services
IND	investigational new drug
NDA	new drug application

CHAPTER 1

INTRODUCTION

Congressman James H. Scheuer, as Chairman of the Subcommittee on Natural Resources, Agriculture Research, and Environment, House Committee on Science and Technology, requested that we report on the status and effectiveness of the Food and Drug Administration's (FDA's) efforts to reduce the processing time of new drug applications (NDAs).

FDA's lengthy drug approval process and the factors that delay it were discussed in a May 28, 1980, GAO report entitled "FDA Drug Approval--A Lengthy Process That Delays the Availability of Important New Drugs" (HRD-80-64). In releasing that report the former Chairman, Subcommittee on House Science Research and Technology, set the stage for this follow-on review by stating:

> "It is becoming clearer to me that the major problem is not the need for extensive legislation but the need for further oversight to see that deficiencies are corrected and that FDA policies reflect a reasonable approach to bring new drugs expeditiously to our nation's millions of sick and suffering citizens."

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. 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. 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. ~01).

REQUIREMENTS OF THE FD&C ACT 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.

The act defines a new drug 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 (all referred to as sponsors), 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 and submits an investigational new drug (IND) application to FDA to begin clinical testing of the compound in humans. 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 an NDA, which, if approved, permits 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 is comprised of 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 biopharmaceutic 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 the application 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 first required to approve the effectiveness of new drugs, it has reviewed over 18,000 applications for investigational use of new drugs. Between 1962 and 1980 FDA

approved 1,271 NDAs. It must be recognized that not all IND applications are subsequently filed as NDAs.

PREVIOUSLY IDENTIFIED DELAYS IN NDA REVIEW PROCESS

In our 1980 report, we concluded that FDA's approval process was lengthy--taking an average of 20 months to approve drugs--and that it often took almost as long to approve an important drug as to approve drugs of less importance. FDA considers a new drug important if it provides a major or modest therapeutic gain over any marketed drugs.

Major factors contributing to long approval times were:

--Imprecise FDA guidelines, subject to varying interpretations.

--Scientific and professional disagreements between FDA and industry.

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

--Lengthy chemistry and manufacturing control reviews.

--Limited time spent by FDA staff reviewing NDAs and an uneven workload among FDA staff.

--Incomplete NDAs and industry's slow rate of resolving deficiencies.

Other factors identified in our 1980 report which seemed to contribute to the long review time included intense congressional and consumer scrutiny of the drug approval process, adversarial relationships between FDA and the drug industry, and FDA's conservative approach to drug regulation.

FDA recognized its lengthy review process needed to be speeded up and in October 1978 set a goal to reduce its processing time over a 3-year period and proposed administrative initiatives to achieve this. (See p. 11.)

OBJECTIVES, SCOPE, AND METHODOLOGY

At the request of the Chairman, Subcommittee on Natural Resources, Agriculture Research, and Environment, House Committee on Science and Technology, we reviewed FDA's efforts to speed up the drug review process.

As agreed with the Chairman, we concentrated our efforts principally on three areas. Our specific objectives were to analyze (1) recent NDA approval data to determine whether FDA was making progress in speeding up the process, (2) recent FDA initiatives aimed at speeding up the drug review process to determine the status of their implementation, and (3) other suggestions that have been made to speed up the drug review process and determine the extent to which they might be implemented by FDA.

To determine the extent to which recent approval data reflected any progress in FDA's efforts, we compared the time required to approve NDAs that were received by FDA during fiscal years 1976 and 1977 with the time required to approve those received during fiscal years 1979 and 1980. We took the number of NDAs received during fiscal years 1976 and 1977 and obtained information on those which FDA had approved as of July 31, 1978, and compared this with the number of NDAs received during fiscal years 1979 and 1980 which FDA had approved as of July 31, 1981.

To achieve its goal set in October 1978, of reducing NDA processing time, FDA implemented a number of initiatives to improve the speed at which drugs are reviewed. We examined a list of FDA's initiatives and, after discussing them with the agency, selected six which appeared to be among the most important. We then focused on the six initiatives to determine the extent to which each was being implemented and likely to have a positive impact in speeding up the drug review process.

Our discussions with FDA officials and other knowledgeable persons (e.g. representatives from industry and former FDA regulators) about the drug review process disclosed that many suggestions had been made by a variety of sources as to how the drug approval process could be improved and speeded up. We concentrated on those that appeared to have the most merit.

Since a number of suggestions for speeding up the drug review process will apparently be dealt with in FDA's rewrite of its new drug approval regulations, we asked to review a draft of this document. FDA advised us that, as of August 1981, the proposed regulation rewrite had not been reviewed by the Commissioner of FDA or the Secretary of Health and Human Services (HHS). For this reason, we concentrated on interviewing cognizant FDA officials to determine their views about the actions FDA would likely take to implement many of the suggestions that had been made. It must be recognized, therefore, that the opinions given by these staff members do not represent the official position of either FDA or HHS and that until the new drug regulation rewrite is officially released for public comment, we cannot be certain of the specific actions FDA is likely to take to speed up the drug review process.

CHAPTER 2

FDA IS MAKING PROGRESS TO REDUCE NDA REVIEW TIME, BUT PROGRESS HAS BEEN INCONSISTENT AMONG REVIEWING DIVISIONS

FDA has made progress in speeding up the drug review process. In 1978, FDA recognized that its lengthy drug review process needed to be speeded up and made a commitment to do so. Our analysis of comparable time periods showed that FDA approved more drugs originally submitted in fiscal years 1979 and 1980 then it did in 1976 and 1977 despite an increased workload. (See p. 6.) The greatest gains were made in reducing processing times of drugs FDA has classified as important.

Although processing times for all drugs decreased in total, progress among FDA's reviewing divisions has not been consistent and some divisions have increased their processing times. Additional emphasis and management scrutiny in these instances is needed and may provide opportunities to further reduce processing times.

To more readily assess its progress in reducing processing times, FDA needs to improve the reliability of its computer data on NDA processing times. Presently, many analyses must be manually performed. Better data would enable FDA to more easily monitor its progress and take any necessary corrective action.

FDA's progress as shown by our analysis should not be used as an absolute measure of the reductions in processing time that may ultimately occur. Additional time and analyses of larger numbers of NDAs are required to more accurately measure FDA's progress.

AVERAGE NDA APPROVAL TIME HAS DECREASED

In October 1978, FDA set a goal to decrease NDA approval time by reducing its processing time for NDAs by 25 percent for important drugs and 15 percent for all others over a 3-year period. As of July 31, 1981, FDA was substantially exceeding its goal for important drugs. For all other drugs the agency had reduced its processing time by 10 percent while substantially increasing the number of NDAs it had approved. Chapter 3 contains our assessment of FDA's initiatives directed at reducing processing time.

To determine FDA's progress in reducing its processing time, we compared processing times for all NDAs originally received in fiscal years 1976 and 1977, and which were subsequently approved by FDA, with those received in fiscal years 1979 and 1980 and also subsequently approved. As shown in the table on page 6, important

NDAs received in fiscal years 1979 and 1980 which had been approved as of July 1981 were processed by FDA in an average time of 10.0 months or 5.7 months (36 percent) faster than similar NDAs received in fiscal years 1976 and 1977 which had been approved as of July 1978. In total, approval time decreased 6.5 months. In addition to reductions in FDA review time, industry reduced the time it took to supply FDA with more data or to answer FDA questions regarding information in the NDA by 0.8 months. FDA approved 15 important NDAs in the pre-1978 period and 17 important NDAs in the post-1978 period.

During the same period, FDA was able to reduce its processing time for other drugs by 1.2 months (10 percent) while increasing the number of NDAs approved. In total, approval time decreased 0.9 months. Although FDA decreased its review time of these drugs by 1.2 months during this period, industry increased the amount of time it took to supply FDA with additional data or answer FDA's questions about NDA by 0.3 months. In fiscal years 1976 and 1977 FDA approved 58 NDAs in this category. In fiscal years 1979 and 1980 this number increased by 79 percent to 104.

Comparison of NDAs Received and Approved in Fiscal Years 1976-77 and 1979-80

Category	NDAs received (note a)	NDAs approved	Approval rate	Average time to approve: Total time	FDA time	Industry time
			(percent)	(months)		
Important drugs:						
1976 and 1977	35	b/15	43	b/17.1	15.7	1.4
1979 and 1980	41	c/17	41	c/10.6	10.0	.6
Increase or decrease (-)			2	-6.5	-5.7	-.8
Other drugs:						
1976 and 1977	197	b/58	29	b/13.2	11.8	1.4
1979 and 1980	239	c/104	43	c/12.3	10.6	1.7
Increase or decrease (-)			14	-.9	-1.2	.3

a/The number of NDAs received was adjusted to exclude NDAs which were not appropriate to the analysis, such as NDAs FDA refused to file because they were incomplete, were later transferred to another Bureau, were canceled, or that could not be approved because of pending litigation.

b/As of July 31, 1978.

c/As of July 31, 1981.

PROCESSING TIME IN SOME DIVISIONS HAS INCREASED

Four of FDA's six reviewing divisions showed an increase in NDA approval time. Of the four divisions showing an increase, two showed a reduction in the number of drugs approved; one showed a slight increase; and one showed a significant increase in the number approved. Two of the six divisions have reduced the time required to approve NDAs. One of these also showed a significant increase in the number of NDAs approved.

The reviewing divisions that increased processing times were Cardio-renal drug products, Neuropharmacological drug products, Oncology and radiopharmaceutical drug products, and Surgical-dental drug products. Their performance is compared below to the two other divisions.

NDA Approvals and Processing Times for FDA Divisions
Average FDA Processing Time

	FY 1976-77		FY 1979-80		
	NDAs approved as of 7/31/78	Months required for approval	NDAs approved as of 7/31/81	Months required for approval	Difference in approval time (months)
Divisions that increased drug approval time:					
Cardio-renal drug products	7	14.8	9	20.0	+5.2
Neuropharmacological drug products	13	10.3	4	13.4	+3.1
Oncology and radiopharmaceutical drug products	10	20.6	4	20.8	+0.2
Surgical-dental drug products	13	10.7	50	11.9	+1.2
	43		67		
Divisions that decreased drug approval time:					
Metabolism-endocrine drug products	10	14.6	35	8.0	-6.6
Anti-infective drug products	20	14.6	19	13.9	-0.7
	30		54		

The Deputy Associate Director for New Drug Evaluation in FDA's Bureau of Drugs told us that several factors contribute to the longer processing times of some divisions. For example, three of the four divisions showing an increase in processing time (all except Surgical-dental) received 50 (71 percent) of 70 original NDAs categorized as new molecular entities (the innovative drugs) in fiscal years 1979-80. In fiscal years 1976-77 these divisions had 41 (59 percent) of 69 original NDAs in this category. According to the Deputy Associate Director, such NDAs are the most complex and time consuming to review. He also said that other factors influencing processing times are workload per reviewer, number of clerical staff, proficiency of reviewers, and willingness of supervisors to delegate work to others. The Deputy Associate Director said he has not determined to what extent each of these factors is responsible for the increased processing times of the divisions.

MEASUREMENT OF PROGRESS IS HAMPERED BY UNRELIABLE COMPUTER DATA

Although information on NDA processing time is computerized, it cannot be used to analyze FDA's progress in approving drugs because it is unreliable. In answering our request for computerized information on NDAs submitted in 4 fiscal years, FDA manually verified all of the computer information and found numerous errors. As a result, all of our computations and analyses had to be manually derived and verified.

This was not the first time that FDA found errors in its computer data and had to verify the data and manually perform the analysis. Rather, an FDA official told us that he routinely does this for reports involving NDA approval times that are prepared for the Secretary of HHS and the FDA Commissioner.

In commenting on our report, HHS stated that the Bureau's computer data base will be improved to the extent possible under current budgetary constraints. HHS said that FDA has already initiated steps to permit so called "on-line" entry and editing of data and expects that this will significantly improve accuracy and facilitate analysis of such data.

CONCLUSIONS

FDA's efforts to speed up the drug review process can be measured in various ways. Comparing approval rates and times at various intervals is only one technique that can be used. We believe FDA needs to revise its system to measure its progress in reducing NDA review time. In this regard, FDA should consider continuing the type of analysis used in this chapter to measure its performance. With access to accurate computerized information, FDA managers can quantitatively analyze their progress from a historical

perspective for the agency as a whole and for each operating division. In doing so, they can determine the amount of progress being made to achieve goals and objectives.

Before revising its system, however, we believe FDA must develop an accurate, computerized data base from which to work. To manually verify computerized data before using them, as FDA did to comply with our request, is time consuming and wasteful. The cost to manually verify the data was not readily available. Manual verification defeats the basic purpose behind having a computerized system.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We recommend that the Secretary direct the FDA Commissioner to:

--Revise its system used in measuring FDA's progress to provide for the types of comparisons identified in this report.

--Develop an accurate computerized data base on which such a system would draw by correcting the errors in the existing computerized data base.

--Publish annually quantitative data showing approval rates for each type of drug (e.g., new molecular entities, new salts, new formulations, etc.) by each reviewing division, for use by program officials and the Congress.

AGENCY COMMENTS AND OUR EVALUATION

In commenting on our draft report, HHS stated that since October 1978, when it committed to reduce review time of important drugs by 25 percent and all others by 15 percent over a 3-year period, FDA has monitored and reported its performance in meeting these goals. According to HHS, reports have been made on a quarterly basis to the Office of the Secretary. HHS stated that FDA will continue to use the same system in effect today to monitor its progress in achieving its goals. HHS also stated that the adequacy of this system for identifying specific trouble spots and bringing them to the attention of appropriate officials will be reviewed by the Commissioner's recently appointed task force for the Review and Improvement of the Drug Approval Process.

As the Commissioner's task force reviews the adequacy of FDA's system, we believe it should pay close attention to the extent to which the system compares similar data before and after FDA developed its initiatives to speed up the drug review process. In this respect, we believe that the system should provide for a comparison of approval rates on NDAs which have been submitted to FDA

during comparable periods of time before and after initiation of FDA actions.

HHS agreed, in part, with our recommendation to publish data annually showing approval rates for each type of drug by each reviewing division. HHS said FDA currently accumulates and uses performance data on each new drug evaluation division for management purposes. HHS advised us that, because applications for different drugs at different points in time vary greatly in complexity and quality, FDA believes that reports on the small number of applications reviewed by individual divisions and comparisons among divisions are meaningless and can be misleading. HHS said that the Commissioner's task force will review the data presently published and the advisability of including more specific information.

We share FDA's concern about small numbers tending to make such reports meaningless. We believe, however, that this type of data will become more meaningful if it is reported continuously for a number of years so trends can be identified and studied. As time passes and more data become available, possible differences in complexity and quality among drugs should become less and less of a problem. Furthermore, our recommendation is based on the premise that HHS will revise its system to allow for valid comparisons of FDA's progress before and after 1978 as discussed above. We believe that this type of system would make published data on each division's review time useful in showing the progress made by each division since October 1978.

CHAPTER 3

FDA'S INITIATIVES TO EXPEDITE DRUG REVIEW HAVE BEEN PARTIALLY SUCCESSFUL

FDA's efforts to expedite the drug review process have achieved some success, but have not eliminated many of the obstacles which prevent more timely review and approval of NDAs. This chapter concentrates on 6 of 21 1/ initiatives undertaken by FDA to achieve the goal it established in October 1978 to reduce drug review time. The six initiatives represent those which we and FDA consider to be among the most important. The status of each of these initiatives is as follows:

--End-of-phase-II conferences, which are designed to better communicate to NDA sponsors FDA's requirements for expanded clinical trials for important new drugs, have been enthusiastically endorsed by most of the companies that have participated in such conferences.

--Pre-NDA submission of manufacturing and controls information, which gives chemists an opportunity to review such information before an important NDA is fully prepared and submitted to FDA, is a technique which has the potential to speed up the drug review process, but one that has been rarely used.

--FDA's priority review system, which is supposed to identify important new drugs for expeditious processing, is misunderstood by some FDA staff and has not been consistently applied.

--FDA's efforts to speed up methods validation, which involves an FDA laboratory attempting to duplicate a sponsor's methods to test a drug's identity, quality, strength, and purity, have been delayed by a lack of clear agreement as to what validations should involve and what data should be provided to laboratories.

--FDA's efforts to improve the timeliness of the work of the Division of Biopharmaceutics, which reviews studies of the

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1/ FDA initially established 20 initiatives to expedite drug review. One initiative dealt with both the Division of Biometrics and the Division of Biopharmaceutics. Because these divisions are involved in different aspects of NDA review, we agreed with FDA officials to treat efforts to expedite these divisions' reviews as distinct initiatives.

drug's behavior in the blood, have been less than totally successful because data requirements of the Division are not being adequately communicated to NDA sponsors and requests for reviews are not being made until late in the NDA review phase.

--FDA's efforts to expedite reviews by the Division of Biometrics, which reviews statistical data in the NDA, also need to go further in informing NDA sponsors of the Division's statistical requirements and in insuring that requests for these reviews are made early in the NDA review process.

Each of these initiatives is discussed in greater detail below. In addition to these initiatives, FDA is revising its NDA regulations. This effort is discussed in chapter 4.

END-OF-PHASE-II CONFERENCES HAVE IMPROVED COMMUNICATIONS WITH INDUSTRY

Clinical testing of new drugs is conducted in three phases:

--Phase I, clinical pharmacology, involves the initial introduction of a drug in humans.

--Phase II, clinical investigation, involves small controlled clinical trials.

--Phase III, clinical trials, involves expanded trials of the drug in larger numbers of test subjects.

FDA invites sponsors of commercial INDs that represent important or modest therapeutic advances to participate in conferences at the end of phase II. These conferences focus on the results of phase I and II studies and the protocol to be followed during phase III of the testing process. The objective of the conference is to speed up the drug's development during phase III by assuring the sponsor that phase III work will be acceptable to FDA. As of April 10, 1981, FDA had conducted end-of-phase-II conferences with 24 drug firms and had invited an additional 18 to participate in such conferences when they completed phase II clinical testing.

To determine how drug firms viewed the effectiveness of the conferences, we contacted 30 firms that either participated in or agreed to participate in end-of-phase-II conferences. Those who participated characterized the conferences as excellent and helpful in identifying FDA's concerns. Officials from 29 of the 30 companies told us they strongly supported the conferences. Fourteen officials told us FDA responded candidly in providing feedback on study design. Examples of industry officials' comments follow.

--One official said: "* * * the meeting with the cardio-renal drug products division was exceptional and very productive. The discussion helped clear up questions FDA had on study design * * * FDA not only raised questions about the study design but also provided helpful suggestions to solve them."

--Another company official considered the 8-month approval time for his NDA faster than average and he believed that conferences held with the anti-infective drug products division contributed to the speedy drug approval.

--Regarding a meeting with the neuropharmacological drug products division a company official said: "Everyone from the company who participated in the conference found it very useful. They were pleasantly surprised at the FDA cooperation and responsiveness."

Two industry officials we talked with, however, expressed concern that some FDA reviewers' requirements for statistical information and analysis constituted a "mini" NDA submission requiring much time, cost, and effort to develop and appeared to be excessive and of limited value to the company. One industry official expressed concern that FDA officials had not adequately prepared for a meeting and did not appear familiar with the information submitted by the company before the meeting.

PRE-NDA SUBMISSION OF MANUFACTURING AND CONTROLS DATA HAS POTENTIAL TO HELP SPEED UP DRUG REVIEW, BUT FIRMS RARELY DO SO

Drug companies may submit manufacturing and control data for new molecular entities classified as important before submitting a complete NDA, but rarely do so. The manufacturing and controls data in an NDA include a description of a drug's components and composition, and the methods, facilities, and controls for manufacturing, processing, and packaging the drug. An FDA chemist reviews these data, and is supported by FDA laboratories, which validate the sponsor's analytical method (see p. 17), and by FDA's Office of Compliance, which determines whether manufacturing facilities are in compliance with good manufacturing practices. FDA has recognized that the manufacturing and controls reviews often add to the time to approve drugs. In December 1978, FDA therefore requested industry to submit the manufacturing and controls part of the NDA for important drugs before submitting the full NDA. The purpose of this initiative is to allow an earlier chemist's review, so that this part of the NDA review would not delay final approval.

As of July 12, 1981, FDA had identified 37 firms eligible to submit manufacturing and controls data before submitting their

fully completed NDAs. As of that date, 11 firms had submitted NDAs but had not presubmitted manufacturing and controls data. A total of six firms did submit such data before submitting an NDA.

Office of New Drug Evaluation officials believe sponsors often choose not to presubmit manufacturing and controls data because they do not make final decisions on the dosage form for manufacturing the actual drug product until they are almost ready to submit the NDA. In addition to this, some sponsors may not be aware that they are sponsoring drugs for which early submission of these data is desired. In establishing its initiative to request industry to presubmit manufacturing and controls data, FDA said that applicants of important drugs would be notified during phase III that early submission of these data is desired. FDA has notified only three firms, however, that they had an IND for which presubmission of manufacturing and controls data was desired. Instead of notifying the other firms when they have drugs for which presubmission is desired, FDA has relied on the Pharmaceutical Mnaufacturers Association to generally make its members aware of this policy.

FDA chemists who reviewed five of the six NDAs for which manufacturing and controls data were submitted early advised us that presubmission of these data expedited the review in some cases, but slowed it down in others. These chemists noted that presubmission can expedite the drug's review if the information submitted is complete and represents the firm's final decision on manufacturing and controls. If, however, the information is incomplete and is changed by the sponsor when the full NDA is submitted, the chemist may have to duplicate much of the review.

One chemist who reviewed two of the drugs for which such data were presubmitted found that one early submission was complete and virtually unchanged in the full NDA submission. The chemist found the manufacturing and controls data for this NDA approvable within 4 months after NDA submission. In contrast, the data were incomplete for the other drug and subsequently changed in the formal NDA submission. The chemist took 9 months to find this NDA's manufacturing and controls data approvable. The chemist attributed the longer time in this case to the fact that initial data were incomplete and the sponsor changed the data in the final submission.

PRIORITY REVIEW POLICY NEEDS TO BE DEFINED IN WRITING AND BETTER COMMUNICATED

To reduce processing time of important NDAs, FDA established an initiative to give them "priority review." FDA has not, however, defined this policy or the means for reviewers to implement it in writing but has instead relied on oral communication. Many

reviewers told us that they have not understood how the priority review policy is to be implemented. Therefore, while some reviewers give important drugs high priority and make every effort to expedite their review, others do not, and treat all NDAs on a first-come, first-served basis.

FDA officials have stated their policy on priority review of important drugs in various public forums. In May 1980, the Deputy Director of the Bureau of Drugs, in addressing a Food and Drug Law Institute conference, said that:

> "throughout the IND and NDA review 'A' and 'B' drugs enjoy a 'red carpet' treatment designed to move them through the evaluation process as expeditiously as possible. It is important to point out that the Priority Review, or 'fast tract' if you will, does not imply a shortened, less thorough, or otherwise abbreviated review. It means solely that once identified, the drug is given special attention so that problems are identified and handled as rapidly as possible."

To implement this priority review policy the Deputy Associate Director for New Drug Evaluation told us that division directors and group leaders--medical officers responsible for supervising reviewers (the chemists, pharmacologists, and medical officers) in their review team--set priorities for reviewing pending drug applications. He said reviewers are to begin reviewing important drugs ahead of other drugs unless the other drugs are in danger of exceeding the 180-day statutory requirement. (See p. 2.) Although FDA has not developed a written policy on priority review requirements, he said he is confident that reviewers have been made aware of the requirement through oral communication.

We interviewed 41 chemists and medical officers who were responsible for reviewing important NDAs originally received in fiscal years 1979 and 1980. Thirty-three told us that they set their own priorities in determining the order in which they review pending NDAs. Moreover, many advised us that they do not understand how the policy is to be implemented. Fourteen told us they were unaware that important drugs were to be reviewed ahead of others and that they review drugs in the order received regardless of therapeutic classification. Twenty-seven said they know of the policy and that they begin their review of important drugs ahead of other drugs. We were unable to determine from FDA's records when reviewers began their reviews of important drugs.

Some reviewers who said they begin their review of important drugs ahead of others also said they take additional steps to expedite the review of important drugs. For example, while FDA often waits until all reviewers have completed their reviews before notifying the drug firm of deficiencies--particularly if the

deficiencies are major--some reviewers said they notify sponsors by telephone immediately when major deficiencies are found. In addition, although FDA guidelines call for chemists to request methods validations and plant inspections by the 75th day after NDA receipt--if NDA approval appears likely--some chemists said they request these services earlier in the review for important drugs. These chemists advised us that they make these requests before determining whether the drug appears approvable, because they know that methods validations and plant inspections may take a long time.

Without a written policy requiring that priority actions be taken, some important NDAs may not be reviewed as expeditiously as possible. We examined FDA records and found the following two examples that illustrate how failure to notify a sponsor promptly of deficiencies and to request methods validation and plant inspection early in the review resulted in delaying the NDA review.

The first example involves an NDA whose sponsor recently decided to discontinue pursuing its approval. However, the events up to that point illustrate how failure to contact the firm promptly of deficiencies can increase NDA processing time.

FDA initially received the NDA on September 23, 1979, and found it approvable, pending validation of methods, 16 months later on January 22, 1981. FDA records show that the chemist and medical officer completed their reviews by the end of November 1979, and noted deficiencies that needed to be corrected. The pharmacologist completed his review by the end of December 1979 and found no deficiencies. FDA did not notify the drug firm of the deficiencies until February 29, 1980, more than 3 months after the chemist and medical officer reviews were completed. The review chemist said that no policy existed to prevent him from notifying the firm of deficiencies immediately after completing his review, but he did not feel a 3- to 4-month delay in notifying the firm of deficiencies was either inordinate or unusual. He said that he considered these deficiencies major, and that he waits until the medical and pharmacology reviews are also complete before notifying the sponsor of major deficiencies. Five months later, on July 23, 1980, the drug firm responded to the deficiencies noted by FDA. Within 1 month after receiving the drug firm's response the medical officer determined the application to be approvable. The chemist completed his review of the firm's response within 1 month but then requested a plant inspection and methods validation. Although the plant inspection was approved within 10 days, the methods validation had not been completed as of April 30, 1981--over 7 months after it had been requested. The FDA laboratory was unable to validate the method as it was written by the drug company. Representatives of FDA and the firm tried to resolve these problems by telephone and through

a meeting between the laboratory and drug firm representatives in April 1981. After this meeting, the firm decided to discontinue seeking approval of the NDA.

The second example involves an NDA for Diopine, an important antiglaucoma drug that FDA received on December 15, 1978, and approved over 16 months later on May 2, 1980. This example illustrates how failure to promptly request methods validation and plant inspections delayed approval of an important drug.

The medical officer and pharmacologist found Diopine approvable in 4 months and 6 months, respectively. The chemist and statistician, however, completed their first review in July 1979, 7 months after the NDA was received. The reviewers promptly notified the drug firm of the NDA deficiencies in a meeting with the firm that month. The chemist told us that he was delayed in completing his review because of competing priorities from other work. We did not discuss why the statistician did not complete his review until July.

The drug firm corrected the deficiencies and submitted an amendment to the NDA on September 19, 1979. The chemist did not, however, request a methods validation and plant inspection until December 26, 1979 (3 months later), when he had substantially completed his second review and found the NDA approvable pending the results of methods validation and plant inspection. Although the statistician completed his second review in January 1980 and found the NDA approvable, the methods validation and plant inspection were not completed until April 22, 1980. FDA approved the drug 10 days later on May 2, 1980.

It appears that earlier requests for methods validation and plant inspection might have led to faster approval of this important NDA. The chemist said that a quick review of the original NDA would have revealed that it contained sufficient information for him to request the validation and inspection as soon as the NDA was received in December 1978. He said that he did not request these services early, because he generally waits until he has completed his review and finds the chemistry and manufacturing control data approvable.

LACK OF CLEAR AGREEMENT ABOUT METHODS VALIDATION CONTINUES TO DELAY NDA APPROVALS

Despite FDA's initiative to speed up validation of analytical methods proposed by drug firms, validations are often delayed and in some instances are the sole factor delaying NDA approval. Methods validation, which is part of the manufacturing and controls review, involves verification by an FDA laboratory of proposed test methods for ensuring the quality, strength, purity, and

identity of drugs. The review chemist requests these validations. To reduce delays and eliminate backlogs of methods validations awaiting verification, FDA redistributed its workload among its laboratories. FDA also established a 45-day goal for verifying proposed test methods. Although FDA has reduced its previous backlog, validations continue to take considerably longer than 45 days. Many delays result from the lack of a clear agreement between validating laboratories and review chemists as to what validations should involve and what data review chemists should provide to laboratories.

As of July 14, 1981, FDA had completed methods validations on 14 of 41 important drugs submitted for review during fiscal years 1979 and 1980. Our analysis showed that methods validations averaged 182 days for the 14 important NDAs. None of the 14 were validated within 45 days. One method was validated in 47 days and another in 62 days. Time required to validate methods in the other 12 NDAs ranged from 104 to 411 days.

FDA officials have indicated in recent public speeches that industry often fails to submit the necessary information required for methods validation. In December 1980, FDA published a study of deficiencies found in analyzing 105 letters which informed sponsors that their NDAs were not approvable. These NDAs were submitted during 1977 and 1978. This study showed that 59 (56 percent) of the 105 NDAs were deficient in methods validation.

While this study indicates that sponsors are not submitting the information FDA considers necessary to validate analytical methods, FDA is partially responsible for this situation. An FDA validating laboratory branch chief told us that review chemists often fail to send the information required to validate testing methods. He said the review chemist either is not aware of what the laboratory chemist requires for a validation or does not agree with the requirement. Therefore, he felt that review chemists do not always assure themselves that the data submitted by industry are complete before submitting the data to the laboratory for validation.

Supervisory review chemists that we interviewed in each of FDA's reviewing divisions confirmed that review chemists and validating laboratories sometimes disagree on information requirements. Of six supervisory chemists we interviewed, five told us that validating laboratories request some information that review chemists consider unnecessary. Two of the supervisory chemists believed that validating laboratories tend to turn methods validations into research projects by reviewing more information than is necessary to approve the drug.

The following example shows a case where disagreement over validation requirements may have delayed the approval of a drug FDA considered to be lifesaving. FDA received this NDA on July 17, 1980, and, according to the division director, gave it priority treatment because FDA considered it to be a breakthrough drug. FDA records show that methods validation was requested on August 22, 1980, about 1 month after the NDA was received. On September 5, 1980, the validating laboratory notified the review chemist that samples of impurities and certain other information were needed to complete the validation. Within 3 days the review chemist requested the information and samples from the drug company which provided them promptly. On October 15, 1980, 2 months after initial receipt of the NDA, the validating laboratory completed its work and found the methods not acceptable. The laboratory requested that the drug firm provide samples of trace impurities that had appeared in a thin layer chromatography test which it had run. FDA records show that the review chemist disagreed with the laboratory on the need for information on the trace impurities and considered the level of impurities to be within the specifications provided by the firm. The review chemist's reasons for disagreeing were as follows:

> "This request is very unreasonable and would create a hardship for the firm if they have to synthesize them (the trace impurity data). The firm has satisfied the requirements of the NDA. They have fully characterized all the potential impurities that they have found.
>
> "In other words, the new substance was reported by the firm to be at least 99% pure. This was confirmed by DDC (Division of Drug Chemistry-the validating laboratory). However, DDC remained adamant in that they wanted these trace impurities.
>
> "In this regard, the decision was made by the reviewing chemist and approved by his immediate supervisor, that DDC has stepped outside of their realm of responsibility * * *."

FDA then decided to obtain another independent validation from a field laboratory. The validation was requested on December 10, 1980, and satisfactorily completed on Feburary 3, 1981.

FDA has recognized the need to clarify its requirements for methods validation, and on March 6, 1981, established a task force to develop guidelines that address four issues:

--Interpreting what the Bureau of Drugs should expect from methods validation.

--Clarifying what information industry should submit as a part of its methods validation data.

--Determining the kinds of products requiring methods validation.

--Specifying the information the review chemists should send to the validating laboratory.

The guidelines are supposed to be ready for Bureau of Drugs review by December 31, 1981. However, the task force chairman told us that draft guidelines will probably not be ready by that time. He said too much controversy still exists between review chemists and representatives from validating laboratories who are members of the task force. He advised us that there are strong disagreements over issues like the need for samples of impurities and the kinds of generic drug products that need to have methods validation. The chairman indicated that these and other disagreements are impeding the efforts of the task force and that it would be a long time before the guidelines would be published.

BIOPHARMACEUTICAL REVIEWS CONTINUE TO BE DELAYED

Efforts to speed up the reviews of the Division of Biopharmaceutics, which reviews such things as the rate of the drug's dissolution in the blood, have not been entirely successful. FDA recognized that biopharmaceutical reviews have contributed to delays in NDA reviews because there was poor coordination between Biopharmaceutics reviewers and other NDA reviewers. To resolve this matter FDA has included Biopharmaceutics representatives in monthly staff meetings to discuss problems they have encountered and the priorities for reviewing various NDAs. In spite of this effort, FDA officials told us that biopharmaceutical reviews continue to be delayed because (1) biopharmaceutical studies are not consolidated into a single section of the NDA, (2) data requirements are not adequately communicated to NDA sponsors, and (3) many requests for biopharmaceutical reviews are not made until late in the NDA review.

Based on an analysis of its NDA reviews in 1977, the Division of Biopharmaceutics found that its reviews were often delayed because relevant studies were scattered through various sections of the NDA and were sent to the Division in a piecemeal fashion by FDA review divisions. The analysis also showed that reviews were delayed by the need to clarify information submitted or to request additional studies from the sponsor.

To address the problem of how biopharmaceutical studies are submitted, the Division proposed a revision to the Federal regulations that would require NDA sponsors to submit all relevant biopharmaceutical studies as a separate section of the NDA. The Office of Management and Budget approved the change (FDA could not determine when), but it was not issued because the Bureau of Drugs decided to delay it until all of its IND/NDA regulation revisions were completed. Delays in issuing FDA's revised IND/NDA regulations are discussed in chapter 4. (See p. 26.)

To minimize the inadequacies in biopharmaceutical studies, the Division has developed guidelines for industry which clarify FDA requirements for conducting, analyzing, and reporting the results of biopharmaceutical studies. A draft of the guidelines was completed in May 1981. The guidelines are undergoing review within FDA and are expected to be issued by spring 1982. Comments from officials of three drug companies we talked with who have reviewed the draft guidelines indicate that the guidelines should help minimize deficiencies in studies submitted for FDA approval. Each of the drug company officials said that the guidelines clarify FDA requirements and formatting preferences. As a result the officials believed that the guidelines, when made available to NDA sponsors, could result in fewer deficiencies and could facilitate the Division's review through better formatting of studies.

Another factor which has delayed biopharmaceutical reviews is the untimely request for these reviews by the Office of New Drug Evaluation. FDA does not have a policy that specifies when in the NDA review phase biopharmaceutical reviews should be requested. For all important drugs received in fiscal years 1979 and 1980 that had biopharmaceutical reviews, requests for these reviews were received an average of 133 days after receipt of the NDA.

According to Biopharmaceutics Division officials, one reason requests for biopharmaceutical reviews are delayed is that relevant studies are scattered throughout the NDA, and it therefore takes time for NDA reviewers in the Office of New Drug Evaluation to identify the studies before requesting a biopharmaceutical review. Division officials said that, when such studies are required as a separate section of the NDA, the review requests should be made earlier.

STATISTICAL REVIEWS CONTINUE TO BE DELAYED

Efforts to speed up the reviews of the Division of Biometrics, which examines the statistical data in the NDA, have not been entirely successful. The statistician conducts his review at the request of a medical officer reviewer who determines which NDAs need a statistical review. FDA recognized that statistical reviews have contributed to delays in NDA reviews because there was

a need to improve coordination between reviews conducted by medical officers and statisticians. To improve the coordination FDA included representatives of the Biometrics Division in monthly staff meetings to discuss problems they encountered and the priorities for reviewing various NDAs. In spite of this, FDA officials told us that statistical reviews continue to be delayed because (1) data requirements of the statistician have not been adequately communicated to NDA sponsors and (2) statistical reviews are not requested in some cases until late in the NDA review phase.

To better inform drug companies of their requirements, Division officials have worked with individual NDA sponsors and participated in various forums attended by industry representatives to explain the requirements. The Division of Biometrics also developed draft guidelines to clarify data requirements and formatting needs for all sponsors and published a notice of availability for them for review and comment in the Federal Register in July 1980. The Division is now revising these guidelines based on the public comments received. The Bureau of Drugs intends to make these guidelines available through the Federal Register when the NDA regulation revisions are issued.

Late requests by the medical officer for statistical reviews have also contributed to delays in completing these reviews. Office of New Drug Evaluation guidelines call for medical officers to request statistical reviews within 45 days after NDA receipt. Many requests for statistical reviews, however, are not made within 45 days. In July 1980, the Associate Director for New Drug Evaluation issued a memorandum to all staff which emphasized this 45-day target for statistical review requests. At the time of our review it was too early for us to evaluate whether this clarifying memorandum has led to more timely requests. The proposed IND/NDA regulation revisions also are expected to provide for statistical data to be submitted in a separate section of the NDA. Division of Biometrics officials believe this will facilitate the ability of the medical officer to submit such data on a more timely basis to the Division.

CONCLUSIONS

FDA's efforts to expedite an NDA review have achieved some success, but have not adequately addressed some problems which continue to delay the drug review. Our analysis of the initiatives that appeared to have the greatest potential to expedite drug review, showed that:

--End-of-phase-II conferences are endorsed by industry and have improved communication between NDA sponsors and FDA on what FDA requires in clinical studies. FDA should continue to encourage sponsors of important drugs to participate in these conferences.

--Pre-NDA submission of manufacturing and controls data can expedite review of important NDAs if the data are complete and in final form. Sponsors, however, rarely submit such data before submitting the NDA. FDA has not notified all firms when they have drugs that are candidates for pre-NDA submissions.

--FDA's priority review system has the potential to speed up the review process of important drugs. FDA, however, has not defined its priority review policy in writing and communicated it to NDA reviewers. Many reviewers are not aware of FDA's requirements for priority review. Additional steps beyond FDA's current requirements appear to have the potential to further expedite the review of important drugs.

--The lack of clear agreement over what is required to perform methods validation could continue to delay validations. Current efforts appear insufficient to resolve this matter.

--Availability of biopharmaceutical guidelines to all NDA sponsors could improve submissions and expedite review of biopharmaceutical information, because they would provide information to drug sponsors on improved formatting and on FDA's biopharmaceutical requirements. Late requests for biopharmaceutical reviews also delay completion of these reviews.

--Data requirements of statisticians in the Division of Biometrics need to be more adequately communicated to NDA sponsors and medical officers need to request statistical reviews earlier in the NDA review process.

RECOMMENDATIONS TO THE SECRETARY OF HHS

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

--Notify applicants individually when they have an IND that is a candidate for pre-NDA submission of manufacturing and controls data, but emphasize that they should presubmit these data only if they are complete and in final form.

--Communicate in writing to all NDA reviewers FDA's priority review requirements. Such requirements should emphasize the need to: (1) begin the review of important drugs ahead of others, (2) notify NDA sponsors of any deficiencies found in important NDAs immediately after the chemist, pharmacologist, and medical officer have completed their respective reviews, and (3) request work from FDA support groups, such as validating laboratories, early in the review process.

--Decide what FDA will require for methods validation, communicate these requirements to NDA sponsors and all FDA review and laboratory chemists, and establish controls to see that these requirements are followed.

--Expedite FDA's review of the draft biopharmaceutical guidelines and make them available to NDA sponsors as soon as this review is completed.

--Establish a guideline for requesting biopharmaceutical studies and see that biopharmaceutical requests are made in a timely fashion.

--Make statistical guidelines available to all NDA sponsors as soon as they are completed.

--Make sure that medical officers involve the Division of Biometrics statisticians early in the NDA review process.

AGENCY COMMENTS AND OUR EVALUATION

HHS concurred with our recommendation that FDA notify applicants when they have an IND that is a candidate for pre-NDA submission of manufacturing and controls data before submitting the full NDA. HHS indicated that it recognized this is effective in reducing review times only if the data are not subject to extensive changes later in the application review. HHS stated that FDA will stress during end-of-phase-II conferences that firms should presubmit such data only when they are reasonably sure major changes will not occur.

With respect to our recommendation on FDA's priority review system, HHS agreed that all reviewers should be notified of the system in writing. In addition, HHS said the Bureau of Drugs will (1) revise its Staff Manual Guide to stress the policy of priority review of those drugs which are believed to afford a therapeutic advance over currently available drugs and (2) distribute copies of the revised guide to all professional staff involved in new drug review. Moreover, the Bureau will monitor adherence to this policy through bimonthly meetings of the Associate Director for New Drug Evaluation with management of each reviewing division.

HHS agreed, in part, that sponsors of NDAs should be notified of deficiencies immediately after each review is completed. HHS stated that, while prompt identification and communication of deficiencies in applications on a discipline-by-discipline basis may have some merit, it does not permit an orderly communication to an applicant of all of the deficiencies in an application and

the Bureau's institutional position concerning whether the application is approvable or not approvable. HHS indicated that such a policy is appropriate for minor deficiencies, but not for major ones. HHS stated that this policy is subject to revision based on the findings of the Commissioner's task force.

Examples discussed in this chapter show that, when individual disciplines notify applicants of major deficiencies, faster review of some important NDAs can result. We therefore continue to believe that FDA should promptly notify NDA sponsors of deficiencies in their applications and that such notification should be beneficial in reducing review time.

HHS agreed with our recommendation on methods validation. HHS advised us that the Bureau of Drugs established a task force in March 1981 to develop guidelines on analytical methods validation for use by NDA sponsors and FDA reviewers. According to HHS, these guidelines will address the kinds of drugs which require validation, the scope of validation activities by an FDA laboratory, the information required by the laboratory to complete the validation, the stage during the review at which the method should be referred to the laboratory for validation, and the time in which the laboratory should be expected to complete its work. Moreover, HHS stated that compliance with the time frames for referrals of validation requests will be monitored by FDA.

HHS agreed to make its biopharmaceutics guidelines available to NDA sponsors after the Bureau of Drugs' current review is completed. HHS plans to issue these guidelines in June 1982. HHS also agreed that reviews of biopharmaceutics studies should be requested in a timely fashion. HHS advised us that FDA intends to revise its regulations to require sponsors to submit a separate section of NDA containing the biopharmaceutics studies. In addition, HHS stated that the Bureau of Drugs will incorporate time frames for review of biopharmaceutics studies in NDAs into a staff manual which will be distributed to all reviewers. Conformance with these objectives will be monitored by FDA.

HHS also agreed that statistical guidelines should be made available to all NDA sponsors as soon as they are completed and stated that these guidelines are in the late stages of development. In addition, HHS agreed that FDA should take steps to ensure early involvement of the Division of Biometrics in the review process. HHS said that FDA will reemphasize to reviewers the need to promptly identify studies needing a statistical review and notify the statistician of these studies.

CHAPTER 4

FDA'S EFFORTS TO REWRITE THE IND/NDA REGULATIONS--A LENGTHY PROCESS WHICH MAY HAVE LIMITED IMPACT ON REDUCING DRUG REVIEW TIME

As early as March 1978, the Commissioner of FDA expressed the agency's intention to rewrite its regulations on investigational new drugs and new drug applications. The Director, Bureau of Drugs, in a public statement in December 1980, said that the proposed revisions of the IND/NDA regulations are undoubtedly the most important activity in the IND/NDA area during the 1980s. As of August 1981 a draft of the regulations had not been released for public comment. FDA officials advised us that a draft of the revised NDA regulations should be published by March 1982 and that it will likely take at least 2 more years before these regulations become final. A draft of the revised IND regulations is not expected to be published for comments until October 1982.

FDA's efforts to speed up the drug review process have been the subject of concern to the Congress, the pharmaceutical industry, and the medical community for a number of years as evidenced in part by the June 17, 1979, hearings before the Subcommittee on Science, Research, and Technology, House Committee on Science and Technology and the September 16, 1981, hearings before the Subcommittee on Natural Resources, Agriculture Research and Environment of the same committee. While it is evident, as pointed out earlier in this report, that FDA is making some progress to speed up the process, we believe that more needs to be done. Changes to the IND/NDA regulations presently being considered could go a long way to help streamline the regulatory process, lessen the amount of detail and supporting documentation required to be filed with an NDA, and improve communication between FDA and NDA sponsors. FDA's efforts to revise these regulations, however, are proceeding very slowly. While many suggestions have been made regarding changes which could speed up the process, FDA has been slow in acting on them.

To determine the types of changes likely to be made in the IND/NDA process, we interviewed FDA officials in the Bureau of Drugs to obtain their reactions to some suggestions for speeding up the drug review process that have been made by various organizations and individuals. On the basis of these interviews it appears that FDA will make some changes that should help improve the efficiency of the drug review process. Other suggested changes have apparently been considered and not entirely accepted. According to the Associate Director for New Drug Evaluation, none of the changes being considered by FDA will revolutionize the IND and NDA process, nor are they expected to cause a dramatic decrease in the time required for NDA approval. FDA officials expect that proposed regulation revisions will cut several months to a year or more off the average 7-year period from the beginning of human testing to approval of a new drug for marketing. The Commissioner will be evaluating the

drug review process to determine whether additional managerial improvements can be effected to improve the overall review and regulation of drugs.

FDA's strategy for revising the IND/NDA regulations was approved by the Commissioner in February 1979. In March 1979 the Bureau of Drugs formed an IND/NDA Rewrite Steering Committee, consisting of several task groups, to oversee the regulation revision project. From March 1979 through June 1981, the Steering Committee met about 40 times, published an IND/NDA concept document, and had several public meetings to discuss and obtain different perspectives on the proposed revisions.

This chapter contains a summary of what appears to be some of the more important suggestions for speeding up the drug review process. The first 11 suggestions were taken from petitions filed with FDA by the Pharmaceutical Manufacturers Association; suggestions 12 and 13 were based on an interview with a former FDA General Counsel. The chapter also discusses the actions, if any, FDA officials believe might be taken on each.

Suggestions to Improve the Time Required to Process an NDA and FDA Reactions

Suggestion	FDA staff comments
1. The NDA Data Should Be Submitted in Sections Tailored to FDA's Different Functional Review Units. Since NDAs are reviewed by five functional review units within the Burea of Drugs--medical, chemistry, pharmacology, biopharmaceutics, and biostatistics--working copies of the NDA should be submitted as separate sections, specifically tailored to the needs of each unit. Applications are currently submitted in three copies and the individual copies are directed within a reviewing division to medical, chemistry, and pharmacology reviewers. We believe this proposed change could reduce the amount of material submitted to FDA and provide each review group with the specific data it needs.	The Associate Director, New Drug Evaluation, Bureau of Drugs, stated in a June 2, 1981, speech to the Drug Information Association that a detailed summary of the data to be reviewed by each of the reviewing specialists, i.e., chemist, pharmacologist, physician, statistician, pharmacokineticist, and microbiologist will be required by the IND/NDA rewrite. New guidelines will provide, in great detail, the format in which FDA would like the data to be prepared.

Suggestion	FDA staff comments
2. The Requirement for the Routine Submission of Copies of All Individual Case Reports With the NDA Should Be Eliminated. Currently, the content of a case report varies depending on the clinical study under investigation. In general, case reports include the following information on each patient: name, medical diagnosis, age, sex, name of drug, amount and frequence of consumption, and adverse reactions. We believe this proposed change could result in the greater use of summary data and comprehensive tabulations which would reduce the volume of data required to be submitted with the NDA and the cost and time involved in preparing and reviewing the NDA.	The Associate Director, New Drug Evaluations, Bureau of Drugs, in a June 2, 1981, speech to the Drug Information Association stated that FDA is seriously considering eliminating the requirement for routine submission of all case reports with the exception of reports involving deaths and dropouts due to adverse events. Under the proposed revision the firm submitting the NDA would have several options. It could (1) submit nothing and wait to be asked for case reports from certain studies, (2) discuss at a pre-NDA submission conference with FDA what case reports FDA would like to see, or (3) submit all or selected case reports on microfiche if the agency agrees to receive them in that form.
3. Mandatory Conferences Should Be Held Before Any Extension of the 180-Day Statutory Limit for NDA Review. An initial conference should be held between the reviewer proposing the extension and the applicant, followed by a second conference between the applicant and the Bureau Director. Section 505 of the FD&C Act provides that an NDA should be approved within 180 days after the filing of an application, unless an additional period is agreed upon by the Secretary and the applicant, or	The Bureau of Drugs advised us that it generally believes requirements for mandatory conferences are overly burdensome because such conferences are not always necessary. The Bureau acknowledged, however, that much confusion surrounds the application of the 180-day statutory time for the agency to review an application and, thus, clarification in the regulations of the 180-day review period is an appropriate subject for the NDA rewrite. FDA advised us in commenting on our draft

Suggestion	FDA staff comments
the applicant must be given a notice of opportunity for a hearing before the Secretary on the question of the application's approvability. In practice, few applications are approved within 180 days of their initial filing. Various mechanisms are used to extend the statutory deadline. For example, FDA considers the date on which an application was resubmitted as the date on which the application is received, thus giving it 180 days from that later date to approve the application or grant another hearing. This suggestion, in our opinion, could insure that the 180-day statutory deadline is extended only when clearly necessary, and establish a written record of the reasons for the extensions.	report, that the revisions to the IND/NDA regulations will clarify the 180-day approval period and under what circumstances that period will be extended. In a June 2, 1981, speech to the Drug Information Association, the Deputy Director of the Bureau of Drugs stated that FDA plans to provide an appeal mechanism for applicants to question or challenge requirements made by FDA staff during the review of an application. The Bureau of Drugs advised us that it intends to establish an environment where differences of opinion in scientific matters can be raised in a manner that both reviewers and applicants find acceptable.
4. A Mechanism for Rapidly Resolving Problems That Arise During the NDA Review Process Needs To Be Developed. According to the Pharmaceutical Manufacturers Association, there are matters of impasse that arise during the review of an NDA which do not warrant advisory committee involvement, e.g., disagreements between the reviewer and applicant on such matters as the need for further animal toxicology tests to support an NDA. Matters not resolved within 30 days should be discussed informally with the applicant;	The Chairman IND/NDA Rewrite Steering Committee stated that, because most problems arise during the IND phase of the review, it will handle this suggestion during the IND rewrite. FDA expects Bureau clearance on the IND rewrite by October 1982.

Suggestion	FDA staff comments
disagreements should be reduced to writing and submitted for supervisory review. There should also be automatic appeals of decisions adverse to an applicant through supervisory channels and ultimate resolution by the Bureau director. This suggestion, in our opinion, could reduce the time required for resolving matters which by themselves have delayed the approval process.	
5. The Office of New Drug Evaluation Should Request and Be Given More Manpower. According to the Pharmaceutical Manufacturers Association, there is a general perception in the drug industry that those divisions within the Office of New Drug Evaluation which have the best ratio of staff to workload also have the best record for prompt review of NDAs. Over the last few years there has been a decrease in the number of persons involved in the actual review of NDAs. We believe this proposed change would reverse the current trend by increasing the number of personnel involved in reviewing drug applications.	In a February 26, 1981, speech to the 50th Business Publications Audit, Inc., Conference, the Deputy Director, Bureau of Drugs, stated that the review process is labor-intensive and will always remain so. The problem FDA faces increasingly is volume overload of its scientific staff. This is occurring at a time when the public and industry want greater efficiency in government and when budgetary constraints appear inevitable. He stated that the solution to this set of problems is to search for new policies and procedures that fundamentally alter the system and to increase the productivity and efficiency of regulatory programs without increases in resources and without increase in risk to the public.

Suggestion	FDA staff comments
6. Coordination Should Be Improved Among the Different Functional Review Groups Within the Bureau of Drugs. In theory the consumer safety officers (CSOs) have responsibility for coordinating efforts, but in fact, the CSOs' relative lack of authority has frequently made them ineffective in resolving problems between the different review units. A member of the review team, such as the medical officer, could be designated as the "team leader" with the responsibility and authority to coordinate the review, synthesize the team's efforts, and present a recommended decision to the division director. This suggestion, in our opinion, would place the NDA coordinating efforts with an individual sufficiently familiar with the details necessary to perform this function.	The Chairman, IND/NDA Rewrite Steering Committee, advised us that the CSOs have many important functions, one of which is to expedite and track NDA documents through the review process. CSOs have no line authority but it is their responsibility to see that unresolved problems are referred to the proper authority for resolution. The Chairman also stated that the IND/NDA format will be tailored to meet the needs of each review unit, which should facilitate and expedite review processing.
7. The Process for Approving Supplements to the NDA Should Be Revised To Permit Additional Changes Without Prior FDA Approval. According to FDA, changes are made in three ways: through supplements that FDA approves before the change can be implemented, through supplements that are submitted when the change is made, and through changes the applicant informs FDA about in the periodic report	In a speech to the Drug Information Association on June 2, 1981, the Associate Director, New Drug Evaluation, stated that under the changes contemplated there will be a marked decrease in the number of manufacturing supplements required to be submitted with NDAs. FDA feels that most supplements which do not require preclearance can be eliminated and firms can notify FDA of the changes made in

Suggestion	FDA staff comments
to the application. Distributor supplements which merely add the name of another distributor to the drug account for 11 percent of NDAs, and 40 percent of those submitted to abbreviated new drug applications (ANDAs). We believe this proposed change could reduce the number of supplements that FDA is currently required to process.	their annual report on the NDA. Supplements for many manufacturing changes now requiring preclearance will also be eliminated. Instead of requiring the submission of these data with the NDA, FDA's inspectors will review any changes during their Good Manufacturing Practices Inspections. In June 1981, FDA eliminated the requirement for distributor supplements. The agency revised its regulations to permit changes in distributors without a supplement provided it is informed about the change in the next periodic report.
8. Questions Arising During the Review Process Should Be Communicated To the Applicant As Soon As Possible Directly From Members of the Reviewing Unit. This suggestion, in our opinion, could provide for more informed communication between FDA and application holders, thereby speeding up the process by which drugs are reviewed by not delaying discussions of important matters until the "not approvable" letter (transmission from FDA that application has been denied) is sent to the applicant.	The Chairman IND/NDA Rewrite Steering Committee advised us that current policy is to communicate promptly to all applicants all deficiencies viewed as major in the "not approvable" letter and all minor deficiencies during the review process. Deficiencies which can be handled without "not approvable" letters are done by telephone. These deficiencies are usually those which can be cleared within 60 days. In commenting on our draft report, HHS advised us that sponsors of NDAs have been ambivalent in their desire to have deficiencies in NDAs

Suggestion	FDA staff comments
	communicated in a "piecemeal" manner. HHS stated that while prompt identification and communication of deficiencies in applications on a discipline-by-discipline basis may have some merit, it does not permit an orderly communication to an applicant of all of the deficiencies in an application and the Bureau's institutional position.
9. Requirements For Reexamining Previously Reviewed Data Should Be Spelled Out in Advance. Studies that have been reviewed by FDA during the IND phase, e.g., toxicology studies, which met all requirements for safety and efficacy, should not routinely warrant additional review during the NDA process. The applicant should be allowed to summarize these studies in the NDA.	FDA advised us that it is considering this comment for improving the drug review process.
10. Manufacturers Should Be Allowed to Voluntarily Withdraw a Previously Approved NDA Without a Finding That the Drug Is No Longer Safe or Effective As Required by Existing Regulations. Under FDA's public information regulations, all information not previously disclosed must be made available to the public upon	Commenting on this suggestion, an FDA staff member assigned to the NDA rewrite group advised us that he agrees with the concept of the suggestion and it will be addressed in the rewrite. According to FDA, the regulation will have to protect the holder's rights.

Suggestion	FDA staff comments
the withdrawal of an approved NDA. This suggestion would allow the holder of an approved NDA to withdraw approval based on a business judgment that the approved drug is no longer commercially viable without subjecting proprietary information to disclosure under the Freedom of Information Act. We believe that withdrawal of such NDAs could eliminate the requirement for the company to submit annual reports to FDA and could relieve FDA staff of the responsibility for reviewing and filing such reports.	
11. The Pharmaceutical Manufacturers Association Believes That Foreign Clinical Studies Which Meet U.S. Statutory Requirements Should Be Considered Fully Acceptable in Demonstrating the Safety and Efficacy of a New Drug and No Additional U.S. Testing Should Be Required. According to FDA, there are several reasons for not approving drugs for marketing in the United States in the absence of some clinical studies performed in this country. The most important is FDA's desire for some experience in the United States of the widespread availability of a drug	In a speech to Business Publications Audit, Inc., February 26, 1981, the Deputy Director, Bureau of Drugs, commented that FDA has had a regulation stating that foreign clinical data are acceptable in support of an NDA since 1975. He stated that during the period 1977-78, 61 of 129 NDAs approved contained information from foreign studies; and in 20 NDAs the foreign studies were considered pivotal for approval. In a March 19, 1981, statement before the American Society for Clinical Pharmacology and Therapeutics, the

Suggestion	FDA staff comments
in this country. We can appreciate why FDA wants some U.S. testing of drugs. However, we believe if research data were truly international, as it is viewed by the scientific community, then the requirement for some U.S. testing should be kept to a minimum.	Associate Director for New Drug Evaluation stated that current regulations require, unless a disease is rare in the United States, at least some studies be performed in this country.
12. FDA Should Make Greater Use of Postmarket Surveillance Studies as a Condition for Approval. Although this process is not discussed in current regulations, NDAs are not uncommonly approved with an agreement by the sponsor that certain studies will be performed after the drug has been approved for marketing.	In a speech to the Drug Information Association June 2, 1981, the Associate Director, New Drug Evaluation, stated that under the proposed revision circumstances under which postmarketing studies would be requested as a condition for NDA approval will be specified. According to the Associate Director, these circumstances may include the need to (1) gather information on a patient population not studied in the pre-NDA approval stage, e.g., children, (2) refine the incidence of certain adverse reactions observed during clinical investigation, and (3) perform studies for a major use which is typical of the drug class but which was not previously studied.
13. FDA Should Eliminate Some of the Reports a Manufacturer Must Submit After an NDA Is Approved. In order to obtain adverse reaction experiences and other data about the use of a drug that may not have surfaced during the preclinical and clinical	In a June 2, 1981, speech to the Drug Information Association, the Associate Director of New Drug Evaluation stated that the proposed revisions will require reporting on an annual basis only and the submission would include only such information for which it is safe to wait a year to report. FDA advised us in August 1981 that it

Suggestion	FDA staff comments
phases of study, the manufacturer of each drug is required to submit periodic reports to FDA. Currently, during the first year after an NDA is approved, firms are required to submit quarterly reports; during the second year semiannual reports; and thereafter annual reports. FDA staff are responsible for reviewing and filing these reports, making sure they are kept current, and for following up on any items that require FDA action. Currently staff must review, file, and keep abreast of matters contained in these reports. We believe this suggestion could eliminate many of these reports and make staff available for other tasks.	intends to require the submission of adverse reaction reports within a period more commensurate with their importance.

CONCLUSIONS

FDA is still working on the NDA rewrite and we had to rely on interviews with cognizant FDA staff to determine the types of changes being contemplated. Based on these interviews it appears that FDA is considering some changes that might speed up the drug review process, including:

--Tailoring applications to FDA's different functional review units.

--Eliminating the requirement that companies submit detailed, individual case reports with each NDA.

--Decreasing the number of supplements that will have to be filed by industry and reviewed by FDA.

--Making greater use of postmarket surveillance studies as a condition for new drug approval.

--Eliminating the requirement for industry to provide FDA with some reports which would decrease the volume of paper flowing to FDA and free reviewers to perform other tasks.

--Improving coordination efforts among FDA's functional review groups.

--Allowing manufacturers more opportunity to voluntarily withdraw previously approved drugs without fear that vital data would be disclosed to competitors. This would free FDA from review and recordkeeping requirements.

There are other suggestions that have been made which FDA apparently has considered and not entirely accepted. We believe, as discussed in this chapter, that some of these could help to speed up the drug review process. These suggestions include:

--Improving procedures to ensure that questions arising during the review process are promptly communicated to the applicant.

--Developing procedures to clarify when previously reviewed data would have to be re-reviewed by FDA.

--Accepting foreign clinical studies which fully meet U.S. statutory requirements without requiring extensive, additional U.S. testing.

--Holding mandatory conferences with applicants before granting any extension of the 180-day statutory limit for NDA review.

Another suggestion that could have an impact on the drug review process but, because of current budgetary constraints, may not be feasible to implement at this time involves increasing staff in the Office of New Drug Evaluation.

It is difficult to determine the extent to which the changes FDA is considering will speed up the drug approval process. Many of the changes are procedural in nature. The extent to which the changes being considered will improve communication between industry and FDA also is unknown and can only be assessed over time. FDA's willingness to accept foreign data seems to be increasing but it appears that the agency will continue to require some domestic verification of foreign studies. While we recognize that some verification may be necessary, we believe that the verification required should be kept to a minimum when foreign studies fully meet U.S. statutory requirements. FDA could require postmarketing surveillance after approval rather than extensive, additional U.S. testing in appropriate situations. FDA may make

some changes to clarify the 180-day statutory deadline requirement; however, the changes contemplated will not provide the applicant immediate access to the Bureau Director before extending the time frame, nor will they establish a written record of reasons for the extensions.

RECOMMENDATION TO THE SECRETARY OF HHS

We recommend that the Secretary direct the Commissioner of FDA to prepare a report to the Chairman, Subcommittee on Natural Resources, Agriculture Research and Environment, House Committee on Science and Technology, detailing each change it has made or plans to make to speed up the drug approval process and estimating the amount of review time the change has saved or is expected to save. The report should address each of the suggestions for speeding up the drug approval process discussed in this chapter, along with any others FDA considers important, and indicate the extent to which the IND/NDA rewrites will address each and, in cases where it disagrees, the specific reasons for disagreement.

Because (1) the Commissioner of FDA expressed the agency's intention to rewrite the NDA and IND regulations as early as March 1978, (2) these revisions will not be ready for public comment until March and October 1982, respectively, (3) FDA agreed that it should continue to be held accountable for the changes it plans to make in the new drug approval process and for estimating their effect on speeding up the process, (4) FDA has indicated that the IND/NDA revisions are the most important activity in this area during the 1980s, and (5) the Congress has expressed much interest in the lengthy drug approval process, we believe that FDA should report to the Congress specific details on what it has done and plans to do to speed up the drug review process.

The report should also contain information on the extent to which reviewers are accepting or rejecting foreign data submitted in support of NDAs and the extent to which additional domestic verification is required. The report should be issued by June 30, 1982.

AGENCY COMMENTS AND OUR EVALUATION

HHS agreed with the intent of our recommendation that FDA should continue to be accountable for the changes it plans to make in the new drug approval process and for estimating their effect on speeding up the process. HHS did not agree that all these plans should be forecast in a report to the Congress by the end of calendar year 1981, as we had suggested in our draft report. Instead, HHS said such a report should be delayed until the Commissioner, his task force, the Assistant Secretary for Health, and

the Secretary of HHS have completed a careful review of the process. HHS advised us that, once the Commissioner's task force and the congressional new drug review commission have issued their reports, HHS will consider preparing a report to the Congress.

FDA's efforts to revise its regulations, issue guidelines, and make general improvements in the drug review process have been delayed in past years while the matter has been studied by the IND/NDA Rewrite Steering Committee. Moreover, many of the problems contributing to delays in the approval of important new drugs are already known to FDA. Some changes contemplated by FDA have been discussed with, and agreed on by, the Pharmaceutical Manufacturers Association, the drug industry, and other interested parties. Furthermore, when one considers that FDA has been working to revise its guidelines and regulations for about 2-1/2 years, we believe that FDA's report to the Congress should have a specific target date. However, in view of the FDA task force and the new drug review commission efforts, we have revised our suggested reporting date so that now we believe that a report to the Congress on FDA's progress should be issued no later than June 30, 1982.

HHS disagreed with our recommendation regarding reporting on the extent to which FDA's reviewers accept or reject foreign data, and the specific reasons for the rejections. HHS stated that assuring that individual reviewers adhere to agency policy is a management issue, which should be addressed by management procedures. HHS indicated that it would not object to including in any report a summary of the contribution of foreign studies to approval decisions on individual NDAs.

We concur that this type of information would be useful but believe that the report should also include information on the extent to which FDA has required domestic verification in those instances where it has accepted foreign studies.

CHAPTER 5

PROPOSED POLICY CHANGE MAY SPEED UP INNOVATIVE DRUG REVIEW BUT DELAY GENERIC DRUG REVIEW

In addition to the initiatives previously discussed in this report, FDA is considering changing the requirements and handling of post-1962 generic drugs--duplicates of innovative drugs already approved and marketed for public consumption. This change would (1) reduce the extent of industry testing and FDA review of drugs whose equivalents have already undergone effectiveness and safety approval by FDA and (2) consolidate the review of generic drugs under one division. If this is accomplished, FDA believes additional industry and FDA scientific personnel will be made available to review and approve--at a faster rate--drugs offering new therapeutic advances. This policy change is also intended to speed up the review of generic drugs which are generally made available to the consumer at less cost than the innovator drug.

We believe that while the policy change may speed the review of important drugs, faster review of generic drugs may not occur because generics now processed by FDA's Office of New Drug Evaluation will be transferred to another Bureau of Drugs division which is experiencing a serious backlog of unapproved applications.

FDA HAS DIFFERENT REQUIREMENTS FOR REVIEWING GENERIC DRUGS

FDA regulations set forth different requirements for generic drugs that duplicate pioneer drugs approved before and after October 10, 1962. FDA's handling of pre- and post-1962 generic drugs was clearly described by the Bureau of Drugs Deputy Director in his February 26, 1981, presentation at the 50th Business Publication Audits Conference. In that presentation, he said that:

> "Prior to 1962 the standard for approval of a new drug application was that the drug be shown to be safe. The 1962 amendments enacted an effectiveness standard for all new drugs submitted to the Agency after that date and required that the Agency determine the effectiveness of all the drug products that had originally been approved and marketed between 1938 and 1962 on the basis of safety only. This process involved evaluation of the effectiveness of these drugs by review of papers in the scientific literature by committees of the National Academy of Sciences and subsequent review by FDA. This whole review is called the DESI--Drug Efficacy Study Implementation--program. If a drug is determined to be effective, that finding is published in the Federal Register and competitor firms can obtain

approval for marketing on the basis of an Abbreviated New Drug Application (ANDA). Clinical and pre-clinical data are not required in ANDA's because safety and effectiveness have already been demonstrated and reviewed publicly under the DESI project. ANDA's eliminate unnecessary human experimentation and expensive, time-consuming clinical trials to obtain safety and effectiveness data on duplicate drugs already well studied. Only manufacturing data and evidence of bioavailability are required.

"The current drug regulatory process does impose a barrier to manufacturers who wish to market a generic drug product in competition with a pioneer drug on which the patent has expired if the pioneer product was approved after 1962. There is no provision for the use of the Abbreviated New Drug Application for generic versions of drugs originally marketed after 1962. Manufacturers of such generic drugs are then faced with getting a full NDA before marketing the product. One reading of the law, which requires "full reports" of the data on a new drug, would suggest that new clinical trials to reestablish safety and effectiveness must be done by the generic manufacturer before he can market the drug. FDA feels that this is scientifically unnecessary, ethically questionable and wasteful of scarce resources for clinical research. Any requirement to 'reinvent the wheel,' so to speak, for a drug for which there is sufficient evidence of safety and effectiveness is simply a barrier to market entry to generic versions of the drug. The Agency has sought to minimize this regulatory barrier to the marketing of post-62 generic drugs by implementing the 'Paper NDA' policy. A new drug application must contain 'full reports' of clinical investigations made to show the safety and effectiveness of the drug. The regulations provide that an NDA may be refused if it does not contain scientific investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports or is represented to have and further that reports of these investigations, among other things, should include adequate information concerning each subject treated with the drug and results of all relevant clinical observations and laboratory examinations. In addition, the 'full reports of clinical investigations' requirement includes submissions of all information pertinent to an evaluation of the safety and effectiveness of the

drug received from any source, including information derived from other investigations or commercial marketing or reports in the scientific literature. The 'Paper NDA' policy provides that the current requirement for submission from the scientific and medical literature. The 'full reports' provision does not, in our view, require reports of original, i.e., new studies by each sponsor. The key studies, however, whether in the literature or unpublished, must be adequate and well-controlled as required by the law, so that the Agency can make a judgment as to their demonstration of safety and effectiveness. An NDA which relies solely on published reports to establish safety and efficacy has come to be known as a 'Paper NDA.'"

In addition to having different requirements for approval, generic drugs are handled by separate units within the Bureau of Drugs. Pre-1962 generic drugs, submitted to FDA as ANDAs, are processed by the Division of Generic Drugs Monographs. As previously discussed, pre-1962 generic drugs need only provide manufacturing and control data as a condition for approval. In contrast, post-1962 generic drugs must satisfy the requirements of a full NDA, which includes providing evidence of safety and efficacy. Post-1962 generic drugs are handled by the Office of New Drug Evaluation.

PROPOSED POLICY CHANGE SHOULD MAKE MORE RESOURCES AVAILABLE TO REVIEW DRUGS OFFERING THERAPEUTIC ADVANCES

Sponsors of post-1962 generic drugs must submit proof of the drug's safety and efficacy. In recent years this meant they had to independently conduct their own animal and human tests or purchase such test data from other manufacturers. That test data then had to be reviewed by FDA medical officers and pharmacologists.

FDA has announced its intent to propose the acceptance of ANDAs for some post-1962 generics. This proposal will be published separate from that of the NDA rewrite regulations. Under this policy applicants would not have to submit animal and clinical evidence of the drug product's safety and effectiveness. The process will be similar to the DESI process for drugs which were marketed before 1962.

Such a policy change would free FDA's medical officers and pharmacologists from reviewing extensive data on generic drugs and would allow them to devote their efforts to drugs affecting therapeutic advances. Since post-1962 generics represented one-half of the Office of New Drug Evaluation's workload, as shown below, the reduction in the amount of medical officer and

pharmacologist time required should be considerable. During the 6-year period ended December 31, 1980, 429 (50 percent) of the 853 NDAs received by the Office of New Drug Evaluation were for generic drugs.

As an interim step to this policy change, FDA has introduced a paper-NDA approach to generic approvals of post-1962 drugs. This interim measure permits sponsors to support their claims of safety and efficacy by citing published literature. This approach also reduces the need for pharmacologists and medical officers to spend their valuable time reviewing generics.

These changes have fostered considerable debates between FDA, manufacturers of the "pioneer drugs," and manufacturers of generic drugs. The principal concern of the pioneer drug manufacturer is that shortened approval procedures will reduce the amount of time they have to market their drugs without competition. They point out that earlier competition from companies which do not incur substantial drug development costs will undermine their ability to recover their own development costs and reap the profits necessary to finance development of other innovative drugs. The pioneer drug companies note further that patent laws cannot be relied on to give them the market monopoly time needed to recover costs and make a profit. This is because the active ingredient is generally patented soon after it is discovered. As a result much of the patent life is exhausted before the drug is marketed.

On the other hand, others see much benefit to be derived from extending the ANDA process to cover all generic drugs. The generic drug industry sees these changes as being beneficial and a means to market drugs without repeating expensive clinical studies. FDA notes that the proposed changes will eliminate unnecessary human experimentation and expensive time-consuming clinical trials to obtain safety and effectiveness data on duplicate drugs which are already well studied. It believes that only manufacturing data and evidence of bioavailability are required. FDA also believes that competition from generic manufacturers will result in lowering the cost of the drugs to consumers.

The Congress is well aware of the benefits of an abbreviated drug approval process as well as the impact such a process can have on the incentive of a drug manufacturer to finance the development of new drugs. This is evidenced by recent hearings before the Subcommittee on Health and Environment, House Committee on Energy and Commerce, on April 1, 1981.

PROPOSED POLICY CHANGE MAY FURTHER DELAY REVIEW OF GENERIC DRUGS

In implementing its proposal to extend the ANDA drug approval process to post-1962 generic drugs, FDA plans to transfer the responsibility for reviewing the post-1962 generic drugs from the Office of New Drug Evaluation to the Division of Generic Drug Monographs. This proposed change will result in an increase in the number of applications for review in the Division of Generic Drug Monographs and a reduction of those submitted to the Office of New Drug Evaluation. The Division of Generic Drug Monographs is already experiencing a serious backlog of ANDAs pending review and this additional workload may aggravate the situation.

In July 1981, the Division of Generic Drug Monographs had 398 ANDAs pending review; 119 (30 percent) of them had exceeded the 180-day statutory review time. (See p. 2.) FDA records show that for January through March 1981, the Division of Generic Drug Monographs was making only marginal gains in reducing its backlog. During that period it received 313 new and resubmitted ANDAs while completing action on 328 ANDAs--a net decrease in its backlog of 15 applications.

As of June 30, 1981, FDA estimated that approval times for ANDAs were averaging about 25 months for 169 applications approved during the first 6 months of calendar year 1981. This, according to the Division Director, is in contrast to ANDA approval times that were averaging less than 12 months prior to December 1979--before backlogs became a serious problem. FDA officials and reports indicated that the large backlog of ANDAs pending review and an inadequate number of reviewers to process this workload were primary factors that contributed to the lengthy approval times.

If FDA adopts its proposed policy change to allow ANDAs for post-1962 generic drugs, the workload of the Division of Generic Drug Monographs will be substantially increased. FDA estimates an increase of between 150 and 435 of such applications within the first year, the majority of which will require some type of biopharmaceutics review. To deal with the present backlog the Division of Generic Drug Monographs is adding more reviewers which the Division Director estimates should be able to eliminate the present backlog within 2 years. On the other hand, the backlog of the Division of Biopharmaceutics has grown from 100 in 1975 to over 400 as of July 1981. The large number of submissions resulting from the implementation of a post-1962 ANDA policy will undoubtedly add to this backlog.

CONCLUSION

FDA's proposed policy change is intended to speed up the approval of drugs offering new therapeutic advances. However, this change may delay the review of generic drugs unless additional reviewers can be provided. If additional reviewers can be found within the agency to assist with the increased workload, the problems discussed above may not occur. Nonetheless, we believe that this situation requires close scrutiny by the Office of the Commissioner and that the information discussed in this chapter should be carefully considered by FDA in implementing its proposed policy.

APPENDIX I

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C 20201

28 SEP 1981

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, "FDA'S Efforts to Speed up the Drug Review Process Are Encouraging--But Progress Has Been Slow and Not Consistent throughout the Agency." 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 P. Kusserow
Inspector General

Enclosure

APPENDIX I

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT:
"FDA'S EFFORTS TO SPEED UP THE DRUG REVIEW PROCESS ARE ENCOURAGING--
BUT PROGRESS HAS BEEN SLOW AND NOT CONSISTENT THROUGHOUT THE AGENCY,"
DATED AUGUST 27, 1981

General Comments

In its report issued May 28, 1980, "FDA Drug Approval--A Lengthy Process that Delays the Availability of Important New Drugs" (HRD-80-64), the Government Accounting Office (GAO) reviewed the Food and Drug Administration (FDA) program for the evaluation of new applications and identified a number of factors affecting the length of the process. GAO made several recommendations to improve the efficiency and speed of the process. Within a few months of completion of that report, the current review was initiated to measure the success of improvements initiated by FDA. As stated in the cover summary of the report, FDA has approved more drugs in less time than before despite an increase in workload; that the greatest reductions in time were made in approvals of important drugs and, in fact, the agency is "substantially exceeding its goal for important drugs." GAO commented that FDA's efforts are encouraging but noted that reduction of approval time has not been consistent throughout all reviewing divisions and offered a new series of recommendations to further reduce the drug review time. The Department appreciates GAO's recognition of FDA's progress to date and agrees that its observations regarding inconsistencies and performance across the six reviewing divisions are valid and that further opportunities are available to reduce drug review time.

The new Commissioner of Food and Drugs, Arthur Hull Hayes, Jr. M.D. is firmly committed to a complete review of the new drug approval process. In order to aid him in this process the Commissioner has recently appointed a 21 member Task Force for the Review and Improvement of the Drug Approval Process. The mandate of this group is to look at and recommend, where appropriate, policy, regulatory, legislative, and management changes to improve the process without lessening FDA's concern for the safety and effectiveness of drugs. The Task Force, which includes members of FDA and other components of the Department, will go beyond past efforts and fully consider wide-ranging matters. The Department shares the agency's concern and will be consulted throughout this process. As a result, the comments made in response to GAO recommendations are subject to reconsideration as the Commissioner, his task force, and the Department give this matter the most careful scrutiny it deserves.

The report observes the ongoing efforts to revise the new drug evaluation regulations. The Department notes that the revision of the new drug application (NDA) regulations is but one element in a series of activities which are intended to examine the policies and procedures of the new drug evaluation process. These include revision of the NDA regulations, revision of the investigational new drug regulations, development of new guidelines to facilitate the submission of the necessary evidence and data on safety, efficacy, labeling and

quality of new drugs, guidelines for reviewers to facilitate the evaluation of these data, review of the administrative processes of the Bureau of Drugs through which new drugs are evaluated, and finally, review of the statutory base of the program to determine if some legislative action is needed.

GAO Recommendations

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

1. —develop a system for use in measuring FDA's progress in meeting its goal of reducing new drug approval time.

2. —develop an accurate computerized data base on which such a system would draw and correct the errors in the existing computerized data base.

Department Comment

As the report notes, the FDA already has and utilizes a system to measure its progress to meet its goals in reducing new drug approval times. Since October 1978, when it committed to reduce its review time of important drugs by 25 percent and by 15 percent for all other drugs over a 3 year period in the Major Initiative Tracking System (now the Operational Management System), FDA has monitored and reported its performance in meeting those goals. Reports have been made on a quarterly basis to the Office of the Secretary. That same system is in effect today and continues to be used by the agency. The agency will continue to monitor its progress in its goal to reduce approval times. However, the adequacy of this system for identifying specific trouble spots and bringing them to the attention of appropriate officials will be reviewed by the Commissioner's task force.

We agree with the recommendation to improve the Bureau's data base with respect to the processing and tracking of approval times and will do so to the extent possible with available resources. FDA has already initiated several steps associated with the revision of its NDA management information system to permit entry of the relevant data required for such purposes through the use of computer terminals (as opposed to the current system using punch cards). This will permit so-called "on-line" entry and editing of the data and should provide for significantly improved accuracy in addition to the manipulation and analysis of such data for further management needs.

GAO Recommendation

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

3. —publish annually quantitative data showing approval rates for each type of drug (e.g., new molecular entities, new salts, new formulations, etc.) by each reviewing division.

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meetings over the past several months. Nevertheless, the Associate Director for New Drug Evaluation sent a memorandum to all reviewers, dated September 4, 1981, directing their attention to the priority review system. In addition, the Bureau of Drugs will revise its Staff Manual Guide on the Drug Classification System to stress the policy of priority review of those drugs which are believed to afford a therapeutic advance over currently available drugs and will distribute copies of the revised guide to all professional staff involved in new drug review. The Bureau will monitor adherence to the priority review system, to the requests for statistics and biopharmaceutics reviews by the Divisions of Biometrics and Biopharmaceutics, and for methods validation by FDA laboratories through its system of administrative rounds (bi-monthly meetings of the Associate Director for New Drug Evaluation and her immediate staff with the management of each reviewing division). Moreover, the Bureau's management will continue to stress the importance of adhering to the priority review system in its "retreats" with Bureau professional staff.

Additionally, we agree in part that sponsors of NDAs be notified of deficiencies found in important NDAs immediately after each reviewer, i.e., chemist, pharmacologist, and medical officer, has completed his/her respective review. As noted by GAO in its previous report, sponsors of NDAs have been ambivalent in their desire to have deficiencies in NDAs communicated in a "piece meal" manner. While prompt identification and communication of deficiencies in applications on a discipline-by-discipline basis may have some merit, it does not permit an orderly communication to an applicant of all of the deficiencies in an application and the Bureau's institutional position, vis-a-vis whether the application is approvable or not approvable. When deficiencies are so significant that the application does not meet the required standards of safety and effectiveness to permit its approval, that institutional decision, in the form of a nonapprovable letter, must be issued over the signature of the Associate Director for New Drug Evaluation and must identify all deficiencies in the application. Where deficiencies are not so substantive that they will result in nonapprovability of an application, they can be, and frequently are, communicated on a discipline-by-discipline basis by the reviewers as an attempt to facilitate the review and expedite a final approvable decision. FDA currently believes this system is preferable to one which would permit each reviewer to communicate all deficiencies in his/her portion of the application independently without incorporating them into a single letter which cites all of the deficiencies in the application, reaches an official agency position, and provides the applicant with recourse to the proper channels of appeal or mechanisms to correct the deficiencies and resubmit the application for further review. Again, however, this policy is subject to revision based upon the findings of the Commissioner's task force.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

6. —Decide what FDA will require for methods validation; communicate these requirements to NDA sponsors and all FDA review and laboratory chemists; and take steps to insure that these requirements are followed.

Department Comment

We concur. FDA recognizes that methods validation continues to be an important determinant in the time required to reach a final decision on the approvability of an NDA. While the agency has made significant changes already in the kinds of drugs for which methods validation is required and in the laboratories to which certain applications are referred, it recognizes that considerable improvement can still be made. As the report notes, the Bureau of Drugs established a task force in March 1981, to develop guidelines on analytical methods validation for use by NDA sponsors and FDA reviewers. These guidelines will address the kinds of drugs which require validation, the scope of validation activities by an Agency laboratory, the information required by the laboratory to complete the validation, the stage during the review at which the method should be referred to the laboratory for validation, and the time in which the laboratory should be expected to complete its work. The methods validation guidelines are but one in a set of manufacturing and controls guidelines which are currently being developed by a series of task forces within the Bureau of Drugs. Once completed, these guidelines will be made available to the industry and distributed to the agency laboratories that participate in methods validation as promptly as possible. Compliance with the time frames for referrals of validation requests will be monitored through the system of administrative rounds noted above.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

7. —Expedite FDA's review of the draft biopharmaceutical guidelines and make them available to NDA sponsors as soon as this review is completed.

Department Comment

We agree that the biopharmaceutics guidelines should be completed and made available to NDA sponsors. These guidelines presently are under review in the Bureau of Drugs to assure that they reflect current policies and accurately identify the nature, number, and kinds of biopharmaceutics studies required to define the necessary parameters to establish a drug's bioavailability. We expect these guidelines to be available in June 1982.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

8. —Establish a guideline for requesting biopharmaceutical studies, and take steps to see that biopharmaceutical requests are made in a timely fashion.

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Department Comment

We concur, in part, with this recommendation. FDA currently accumulates and uses for managerial purposes performance data on each new drug evaluation division. The agency also publishes annually a New Drug Evaluation Briefing Book which reports statistics on various aspects of the new drug evaluation project, including numbers and times of applications approved. At one time, statistics on an individual division basis were included. However, because the applications for different drugs at different points in time vary greatly in complexity and quality, FDA concluded that reports on the small number of applications reviewed by individual divisions and comparisons among divisions are meaningless and can be misleading. The Commissioner's task force will, however, review the data that is presently published and the advisability of including more specific information.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

4. —Notify applicants individually when they have an investigational new drug that is a candidate for pre-NDA submission of manufacturing and controls data, but emphasize that they should pre-submit this data only if it is complete and in its final form.

Department Comment

We concur that FDA should continue to encourage pre-NDA submission of manufacturing and controls information for those new drugs which represent therapeutic advances. As the report notes, however, this is effective in reducing review time only if the manufacturing and controls data are not extensively changed by the applicant later in the application review. FDA will stress to applicants in the End-of-Phase II Conferences that they should submit the manufacturing and controls portions of the application prior to the NDA submission only when they are reasonably sure that major changes will not occur.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

5. —Communicate in writing to all NDA reviewers FDA's priority review requirements. Such requirements should emphasize the need to: (1) begin the review of important drugs ahead of others, (2) notify NDA sponsors of any deficiencies found in important NDAs immediately after the chemist, pharmacologist, and medical officer have completed their respective reviews, and (3) request work from FDA support groups, such as validating laboratories, early in the review process.

Department Comment

We concur that all reviewers should be informed in writing of the priority review system. FDA has repeatedly attempted to inform them in

Department Comment

We agree that requests for review of biopharmaceutics studies should be made in a timely fashion in order that the review may be completed concurrent with reviews of other portions of the application. For the most part, this recommendation will be satisfied by the agency's intent to require a separate section of the NDA containing the biopharmaceutics studies (as recommended in the petition of the Pharmaceutical Manufacturers Association), which will be referred directly to the Division of Biopharmaceutics. When it is implemented, following revision of the NDA regulations, this change will obviate the need for other reviewers to identify and make available to the Division of Biopharmaceutics those portions of the application required for its review. In addition, the Bureau of Drugs will incorporate the time frames for review of biopharmaceutics studies in NDAs into a staff manual guide which will be distributed to all reviewers; it will also monitor conformance with those objectives through the system of administrative rounds. The adequacy and appropriateness of this approach will be reviewed by the Commissioner's task force.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

9. --Make statistical guidelines available to all NDA sponsors as soon as they are completed.

Department Comment

We concur. The statistical guidelines are in a late stage of development and upon completion, in March 1982, will be made available for use by NDA sponsors.

GAO Recommendation

We recommend that the Secretary of Health and Human Services direct the Commissioner of FDA to:

10. --Take steps to insure that medical officers involve the Division of Biometrics statisticians early in the NDA review process.

Department Comment

We concur. As with the biopharmaceutics studies, statistical evaluation of clinical studies in NDAs will be facilitated by a separate volume containing the statistical studies which will be required in the revision of the NDA regulations. Once implemented, the Division of Biometrics will obtain the clinical data and other necessary statistical evaluation and treatments of those data required for its evaluation at the same time the other review disciplines receive the application. In addition, the agency will reemphasize to its reviewers the need to identify promptly those key studies that require statistical analysis and arrange for conferences between the medical officer and statistician reviewers to discuss and agree on the nature of statistical review required. The Bureau of Drugs' statistical and medical officer review guidelines call for such consultation by the 45th review day. Compliance with the

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guideline will be monitored through administrative rounds. This procedure will also be reviewed by the Commissioner's task force.

GAO Recommendation

11. --We recommend that the Secretary of HHS direct the Commissioner FDA to prepare a report to the Chairman, Subcommittee on Natural Resources, Agriculture Research and Environment, of the Committee on Science and Technology detailing each change it has made or plans to make to speed up the drug approval process and estimating the amount of review time each change has or is expected to save. The report should address each of the suggestions for speeding up the drug approval process discussed in this chapter, along with any others FDA considers important, and indicate the extent to which the IND/NDA rewrites will address each and in cases where it disagrees, the specific reasons for disagreement.

The report should also contain information on the extent to which individual reviewers are accepting or rejecting foreign data submitted in support of NDAs and the specific reasons for rejections. The report should contain a timetable for FDA action indicating specifically when FDA intends to implement any action it intends to take. The report should be issued by the end of calendar year 1981.

Department Comment

The Department agrees with the intent of the recommendation that FDA continue to be accountable for the changes it plans to make in the new drug approval process and to estimate the impact of these changes on the process. However, it does not agree that all of these plans should be forecast in a report to be submitted to the Congress by the end of calendar year 1981.

Any such report should await the careful review of the process by the Commissioner, his task force, the Assistant Secretary for Health and the Secretary. In addition, Congressmen Scheuer and Gore are sponsoring the Commission on the Federal Drug Approval Process. Neither of these groups will have completed its work by the end of calendar year 1981. Once these groups have issued their reports, consideration will be given to preparation of a report to the Congress.

With respect to the specific subrecommendation on reporting the extent to which individual reviewers accept or reject foreign data in specific NDAs with the reasons for rejection, the Department does not concur with the recommendation. We believe that such a report would be inappropriate. Ensuring that individual reviewers follow agency policy is a management issue and, where necessary, should be addressed by management procedure. The Department would not object to including in any report a summary of the contribution made by foreign studies to the approval decisions on individual NDAs.

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It is important to keep in mind several points with regard to the use of foreign clinical data:

1. This matter will be carefully reviewed by the Commissioner's task force and the appropriate policy enunciated thereafter.

2. The agency has accepted and continues to accept foreign clinical studies in support of NDAs. As reported by the Associate Director for New Drug Evaluation in her presentation to the American Society of Clinical Pharmacology and Experimental Therapeutics in New Orleans on March 19, 1981, during the 7 year period from 1974 through 1980 of 166 NDAs approved for drugs representing new molecular entities, new salts or esters of molecular entities, and major new indications, more than 50 percent contained reports of studies conducted outside the United States and, in 35 percent, the foreign studies were considered significant and/or pivotal for approval.

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