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STATEMENT OF
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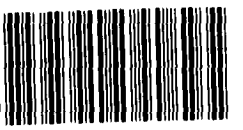
BEFORE THE
SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH
AND ENVIRONMENT, HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY



ON THE
FOOD AND DRUG ADMINISTRATION'S
EFFORTS TO SPEED UP THE DRUG REVIEW PROCESS

Mr. Chairman, and members of the Subcommittee, we are pleased to be here today to summarize and discuss our review of the Food and Drug Administration's (FDA's) efforts to speed up its drug review process. Our prior report of May 28, 1980, to the Subcommittee on Science, Research and Technology indicated that FDA's drug review process was lengthy and that it took almost as long to approve important drugs as drugs of less importance. Our report identified the following factors which we believed affected FDA's efforts to approve drugs in a timely manner:

--FDA guidelines regarding documentation to be submitted with a new drug application (NDA) and the formatting of such documentation were imprecise and subject to varying interpretations.

--Scientific and professional disagreements between FDA and industry were not being promptly resolved.

--FDA feedback to industry was slow or inadequate in notifying firms of deficiencies in NDAs.

--FDA's chemistry and manufacturing control reviews were lengthy.

--Pharmaceutical firms were submitting incomplete NDAs and were slow in resolving deficiencies noted by FDA.

Commenting on that report, FDA said it would take certain actions that it believed would reduce the time required to process NDAs by 25 percent for important drugs and 15 percent for all others over a 3-year period. Our objectives on this review, which was made at your request, were to analyze recent NDA approval data, actions taken by FDA as a result of our prior report, and other suggestions that had been made to speed up FDA's processing time to determine the extent of its progress.

On August 27, 1981, we sent a copy of our draft report on this review to the Secretary of Health and Human Services (HHS) for comment. A copy of that draft was provided to you on August 28 pursuant to your request. The draft has not been fully reviewed within GAO and we have not yet received the agency's comments. Therefore, I would like to caution that the draft, including the recommendations which are discussed in my statement, are subject to revision.

EFFORTS TO SPEED UP THE DRUG REVIEW PROCESS ARE ENCOURAGING--BUT PROGRESS HAS NOT BEEN CONSISTENT THROUGHOUT THE AGENCY

We compared FDA's processing times for all NDAs originally received in fiscal years 1976 and 1977 which were approved as of March 1978 with those received in fiscal years 1979 and 1980 which were approved as of March 1981. As shown in the following table, NDAs for important drugs received in fiscal years 1979 and 1980 were processed by FDA in an average time of 8.2 months, or 6.0 months (42 percent) faster than similar NDAs received in fiscal years 1976 and 1977 which had been approved as of March 1978. In total, approval time decreased 6.6 months. In addition to reductions in FDA's 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 0.6 months. FDA approved 12 important NDAs in the pre-1978 period and 14 important NDAs in the post-1978 period.

Comparison of NDA's Received and Approved
in Fiscal Years 1976-77 and 1979-80

Category	NDAs a/ received	NDAs approved	Approval rate (percent)	Average time to approve: Total time	FDA time (months)	Industr time
Important drugs:						
1976 & 1977	35	12 b/	34	15.5 b/	14.2	1.3
1979 & 1980	41	14 c/	34	8.9 c/	8.2	.7
Increase (Decrease)			-0-	(6.6)	(6.0)	(.6)
Other drugs:						
1976 & 1977	197	48 b/	24	12.1 b/	11.1	1.0
1979 & 1980	239	85 c/	36	11.4 c/	10.0	1.4
Increase (Decrease)			12	(.7)	(1.1)	.4

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

b/As of March 31, 1978.

c/As of March 31, 1981.

During the same period, FDA was able to reduce its processing time for other drugs by 1.1 months (10 percent) while increasing the number of NDAs approved. In total, approval time decreased 0.7 months. Although FDA decreased its review time of these drugs by 1.1 months during this period, industry increased the amount of time it took to supply FDA with additional data or answer FDA's questions about the NDA by 0.4 months. In fiscal years 1976 and 1977 FDA approved 48 NDAs in this category. In fiscal years 1979 and 1980 this number increased by 77 percent to 85.

We would like to caution, Mr. Chairman, that FDA's progress as shown by this analysis is encouraging, but should not be used as an absolute measure of the reductions in processing time that may ultimately occur. As the table indicates many NDAs included in our analysis had not been approved as of March 1981. Additional time and analyses of these NDAs are required to more accurately measure FDA's progress.

Although FDA has improved its processing time, problems still remain. For example, only two of FDA's six reviewing divisions reduced their review time. The other four divisions showed an increase in NDA review time. (See appendix.) One of the four, however, significantly increased the number of NDAs approved.

Because some reviewing divisions have increased their review time, we believe additional management scrutiny of these divisions may provide opportunities to further reduce processing times. Also, FDA needs to improve the reliability of its computer data in order to provide an accurate basis for monitoring its progress.

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 had found errors in its computer data and had to verify the data and manually compute the analysis. An FDA official told us that he routinely does this for reports involving NDA approval times that are prepared for the Secretary of Health and Human Services (HHS) and the FDA Commissioner.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We are recommending that the Secretary direct the FDA Commissioner to

- --develop a system to measure FDA's progress in meeting its goals of reducing new drug approval time,
- --develop an accurate computerized data base on which such a system would draw and correct the errors in the existing computerized data base, and
- --publish annually quantitative data showing approval rates for each type of drug (new molecular entities, new salts, new formulations, etc.) by each reviewing division.

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

Although FDA's efforts to expedite the drug review process have achieved some success, FDA has not eliminated all the obstacles which prevent more timely review and approval of NDAs. We reviewed 6 of 21 initiatives undertaken by FDA to achieve

the goal it established in October 1978 to reduce drug review time. The six initiatives represent those that we and FDA consider to be among the most important. They involve:

--FDA's efforts to improve its communication with industry by conducting conferences at the end of phase II clinical testing.

--FDA's invitation to sponsors of important drugs to submit manufacturing and controls information early before their NDA is fully prepared and submitted to FDA.

--FDA's priority review system to expedite processing of important new drug applications.

--FDA's efforts to speed up its process for validating a sponsor's methods to test a drug's identity, quality, strength, and purity.

--FDA's efforts to improve the timeliness of the work of the Division of Biopharmaceutics, which reviews studies of the drug's behavior in the blood.

--FDA's efforts to expedite reviews by the Division of Biometrics, which reviews statistical data in the NDA.

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; and phase III, clinical trials, involves expanded trials of the drug in larger numbers of test subjects. FDA invites sponsors of commercial investigational new drugs (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. 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 amother 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, 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 said FDA provided candid feedback on study design.

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

FDA has recognized that the manufacturing and controls reviews often add to the time taken to approve drugs. In December 1978, FDA therefore requested industry to submit the manufacturing and controls part of the NDA for drugs classified as important 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. Industry, however, has infrequently submitted its information early.

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, 10 firms had submitted NDAs but had not presubmitted manufacturing and controls data. Only five firms had submitted 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, some sponsors may not be aware that they are sponsoring drugs for which early submission of these data is desired.

FDA's chemists advised us 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, FDA's chemists may have to duplicate much of their review.

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

To reduce processing time of important new drug applications, FDA established an initiative to give them "priority review." Priority review is intended to give important drugs special attention so that their applications are handled as rapidly as possible. FDA has not, however, defined this policy or the means for reviewers to implement it in writing. It has instead relied on oral communication. Many reviewers advised 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.

Although FDA has not developed a written policy on priority review requirements, the Deputy Associate Director for New Drug Evaluation said he was confident that reviewers have been told about the requirement.

We interviewed 41 chemists and medical officers who were responsible for reviewing important NDAs originally received in fiscal years 1979 and 1980. Thirty-three said they set their own priorities in determining the order in which they review pending NDAs. Fourteen told us they were unaware that important drugs were to be reviewed before others and that they review drugs in the order received regardless of therapeutic classification. Twenty-seven said they knew of the policy and that they review important drugs before other drugs.

Some reviewers 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.

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 are sometimes the sole factor delaying NDA approval. Methods validation involves an FDA laboratory verifying proposed test methods for ensuring the quality, strength, purity and identity of a drug. FDA has established a 45-day goal for performing this function.

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 remaining 12 NDAs ranged from 104 to 411 days.

In December 1980, FDA published a study of deficiencies found in analyzing 105 letters in which it 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 were not submitting the information FDA considered necessary to validate analytical methods, we found that FDA was also partly responsible

for this situation. An FDA validating laboratory branch chief told us, for example, that FDA review chemists often fail to send the information required to validate testing methods to the FDA laboratory. He said the review chemists either are not aware of what the laboratory chemist requires for a validation or do 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 them to the laboratory for validation.

FDA has recognized the need to clarify its requirements for methods validation. On March 6, 1981, FDA established a task force to develop guidelines to address (1) what the Bureau of Drugs should expect from methods validation, (2) what information industry should submit as a part of its methods validation data, (3) what kinds of products require methods validation, and (4) what information the review chemists should send to the validating laboratory.

The guidelines were to have been ready for Bureau of Drugs review by September 1, 1981. However, on September 1, 1981 the task force chairman told us that the target date had not been met. He said a revised target of October 1, 1981 had been set and that he expects to have the draft guidelines ready for bureau review at that time.

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 dissolution of a drug in the blood, have not been totally successful.

FDA officials told us that biopharmaceutical reviews are 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. FDA also recognized that poor coordination existed between biopharmaceutics reviewers and other FDA reviewers of NDA material.

Based on an analysis of 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 the need to request additional studies from the sponsor.

Another factor which has delayed biopharmaceutical reviews is the untimely request for these reviews by the Office of New Drug Evaluation. 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 them before requesting a biopharmaceutical review.

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 also not been totally successful. FDA recognized that statistical reviews have contributed to delays in NDA reviews and that improved coordination was needed 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. Nevertheless, 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 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.

In July 1980, the Associate Director for New Drug Evaluation issued a memorandum to all staff emphasizing FDA's 45-day target for statistical review requests. At the time of our review, it was too early to evaluate whether this clarifying memorandum had 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 enable the medical officer to submit such data on a more timely basis to the division.

CONCLUSIONS AND RECOMMENDATIONS TO THE SECRETARY OF HHS

FDA's efforts to expedite NDA review have achieved some success, but have not adequately addressed some problems which continue to delay the drug review. We are recommending 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 the data are complete and in final form.

--Communicate in writing FDA's priority review requirements to all NDA reviewers. 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 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 insure 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 requests are made in a timely fashion.

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

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

FDA'S EFFORTS TO REWRITE THE IND/NDA REGULATIONS

As early as March 1978, the Commissioner of FDA expressed the agency's intention to rewrite its regulations on INDs and NDAs. 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. Yet, as of August 1981 a draft of the regulations had not been released for public comment. FDA has advised us that a draft of the revised NDA regulations should be published by March 1982 and that these regulations will probably not become final for at least 2 more yers.

A draft of the revised IND regulations is not expected to be published for comments until October 1982.

To determine the types of changes likely to be made in the IND/NDA process, we interviewed cognizant Bureau of Drugs officials to obtain their reactions to a number of suggestions for speeding up the drug review process made by various organizations and individuals. On the basis of these interviews, it appears that FDA is considering some changes that should help improve the efficiency of 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 NDAs without fear that vital data would be disclosed to competitors. This would free FDA from review and recordkeeping requirements.

Other suggestions have been made that FDA apparently has considered and rejected. We believe that some of these could similarly 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 that 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.

It is difficult to determine the extent to which the changes that FDA is considering will speed up the drug approval 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. FDA's willingness to accept foreign data seems to be increasing, but the agency will apparently 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. In appropriate situations, FDA could require

postmarketing surveillance after approval rather than extensive, additional U.S. testing.

According to the Associate Director for New Drug Evaluation, none of the changes being considered will revolutionize the IND and NDA process nor are they expected to cause a dramatic decrease in the time required for NDA approval. FDA advised us, however, that it expects proposed regulation revisions to 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. FDA further advised us that 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.

RECOMMENDATION TO THE SECRETARY OF HHS

Because of the importance attributed to the IND/NDA rewrite and the time which this effort has already taken, we are recommending that the Secretary direct the Commissioner of FDA to prepare a report to you, Mr. Chairman, detailing each change it has made or will 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 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 planned action. The report should be issued by the end of calendar year 1981.

PROPOSED POLICY CHANGES MAY SPEED UP REVIEW OF INNOVATIVE DRUGS BUT DELAY GENERIC DRUG REVIEW

In addition to the initiatives discussed, 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 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 change may speed the review of important drugs, faster review of generic drugs may not result because generics now processed by FDA's Office of New Drug Evaluation will be transferred to another Bureau of Drugs division which has a large backlog of unapproved applications. If additional reviewers can be found within the agency to assist with the increased workload delays in reviewing generic drugs may not occur. We believe that implementing this proposed policy change requires close scrutiny by the Office of the Commissioner to assure that unexpected adverse impacts are minimized.

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Mr. Chairman, this concludes my statement. We will be pleased to answer any questions you or other members of the Subcommittee may have.

NDA APPROVALS AND PROCESSING TIMES FOR FDA DIVISIONS

AVERAGE FDA PROCESSING TIME

	FY 1976-1977		FY 1979-1980		
	NDA's approved as of 3/31/78	Months required for approval	NDA's approved as of 3/31/81	Months required for approval	Difference in approval time (In months)
Divisions that increased drug approval time					
Cardio-renal drug products	5	10.4	5	16.2	+5.8
Neuropharmacological drug products	12	9.8	4	11.4	+1.6
Oncology and radiopharmaceutical drug produtcs	5	15.4	3	17.8	+2.4
Surgical-dental drug products	11	9.0	43	10.6	+1.6
	33		55		
Divisions that decreased drug approval time					
Metabolism-endocrine drug products	9	12.1	30	5.7	-6.4
Anti-infective drug products	18	13.8	14	11.6	-2.2
	27		44		