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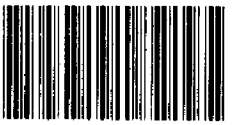
STATEMENT OF
GREGORY J. AHART, DIRECTOR, HUMAN RESOURCES DIVISION
BEFORE THE
COMMITTEE ON SCIENCE AND TECHNOLOGY
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY
ON
THE FOOD AND DRUG ADMINISTRATION'S
DRUG APPROVAL PROCESS



Mr. Chairmen and Members of the Subcommittee, we are pleased to be here today to discuss the results to date of our review of the Food and Drug Administration's (FDA's) process for approving new medical drugs for marketing in the United States.

Our review, as you know, was undertaken in response to a request from the Chairman of the Subcommittee on Domestic and International Scientific Planning, Analysis, and Cooperation which in the current Congress was merged with the Science, Research and Technology Subcommittee. Our review was directed at determining (1) whether there are inordinate delays in processing and approving new drugs for marketing in the United States; (2) whether delays in approving new drugs adversely impact on the introduction into the United States of therapeutically important drugs that are available in other countries; (3) how FDA's drug approval process compares with approval processes of other technologically developed countries; and (4) whether innovative use of computer technology could eliminate inordinate delays in the drug approval process.

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GENERAL BACKGROUND

The Federal Food, Drug, and Cosmetic Act and implementing regulations for investigational use of new drugs require FDA

to exercise close control over the clinical, or human, testing of new drugs. The act requires that, before a new drug may be introduced into interstate commerce, FDA must approve the drug for safety and efficacy.

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

To satisfy FDA requirements for safety and efficacy, a sponsor of a new drug must clinically test the drug under closely controlled circumstances. A sponsor is the person who assumes responsibility for an investigation of a new drug. Sponsors generally fall into three categories: drug manufacturers, private and Government agencies, or individual physicians. The evidence of safety and efficacy obtained from clinical studies is included in a new drug application, (NDA), submitted to FDA by a sponsor who usually is a drug manufacturer seeking to market a new drug product.

The NDA contains: (1) full reports of investigations, including animal and clinical investigations, which have

been made to show whether or not 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 used for, the manufacturing, processing, and packaging of the drug; (4) samples of the drug and components as may be required; and (5) copy of proposed labeling.

To review the data submitted, FDA uses a team of three primary reviewers including a medical officer who reviews the clinical test results, a pharmacologist who reviews the animal test results, and a chemist who reviews the chemistry and manufacturing controls and process. The review teams may also be supported by a microbiologist and a statistician if appropriate.

The law provides that within 180 days after an NDA is filed, FDA must approve it or give the applicant notice of an opportunity for a hearing on the deficiencies found in the application. FDA may take longer than 180 days to decide on an application if the applicant and FDA agree to an additional period of time.

IMPORTANT DRUGS TAKE A LONG TIME TO APPROVE

We noted that processing NDAs takes a long time. The statutory 180-day review time is generally not met. Our analysis shows that the average approval time for original NDAs submitted in calendar year 1975 was about 20 months. FDA's own analysis shows that the average approval time for 80 NDAs approved in fiscal year 1978 was about 34 months. These two analyses differ with

respect to the number of NDAs involved. Our analysis included only NDAs submitted in 1975 and FDA considered all NDAs approved in 1978 some of which were submitted over a period of several years prior to 1978.

NDAs that were involved in the lengthy review process included drugs FDA classified as being therapeutically important, and some of these were available in other countries before they were available in the United States. FDA considers a new drug important if it provides a major or modest therapeutic gain over any marketed drugs. Lengthy approval times for important drugs deprive the general public of the therapeutic advantages of such new drugs and, according to industry officials, adds substantially to the cost of developing the drugs.

A number of drugs submitted to FDA for approval in 1975 and classified by FDA as important took from 12 to 32 months to be approved; half took over 20 months. For example, dobutamine hydrochloride, a drug used for treatment of cardiac decompensation, a form of heart failure, was approved in July 1978, 31 months after it was initially submitted for approval. Another drug FDA classified as important is somatotropin. This drug, which is used to promote growth in children with short stature due to a deficiency of pituitary growth hormone, was approved on July 30, 1976, about 15 months after an NDA was submitted to FDA.

Both of these drugs were available sooner in other countries. Dobutamine was approved for use in the United Kingdom in September 1977. Somatotropin was approved for use in Sweden in 1971 and in the United Kingdom and Switzerland in 1972.

During the period July 1975 through February 1978 FDA approved 14 drugs it classified as important, including somatotropin. Thirteen of these drugs were available elsewhere 2 months to 12 years earlier than they were available in the United States. For example, an NDA for beclomethasone dipropionate, a drug used for the treatment of chronic asthma, was submitted to FDA in February 1974 and approved in May 1976 or 27 months later. This drug was available earlier in Norway, Sweden, Switzerland and the United Kingdom, and was approved in a much shorter period of time in all four countries. The approval times ranged from 4 months in the United Kingdom to 18 months in Sweden.

Other important drugs that were approved for use in other countries before they were approved for use in the United States include:

--Bromocryptine which was approved almost 3 years earlier in Switzerland. It is used to treat an endocrine disorder of the uterus and breast, Parkinson's disease (a nervous system disease common in older people) and acormegaly (an endocrine system disease with a particular affect on the bones).

--Disopyramide which was approved more than 5 years earlier in the United Kingdom. It is used to treat abnormal heart rhythm.

--Propranolol which was approved more than 7 years earlier in the United Kingdom. This drug at the time of its introduction, represented a most important advance in treatment of high blood pressure.

--Sodium valproate which was approved about 11 years earlier in France. It is used to treat epilepsy.

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

Physicians in other countries advised us of several important drugs licensed for use in those countries, which we found have not been approved for use in the United States. Among these are:

--Alprenolol, a drug which was approved in Sweden more than 3 years ago for prevention of death after heart attacks.

--Ancrod, a drug which has been marketed since 1974 in the United Kingdom and used as an anti-coagulant to prevent or treat blood clots.

--Chenodeoxycholic acid, a drug which was approved in 1976 in Switzerland and is used to dissolve gall stones.

--Cyproterone, a drug which was approved 6 years ago in Germany and used in the treatment of sexual hyperactivity and precocious puberty.

Most of these drugs have been approved in the United States for clinical investigations.

According to officials in foreign drug regulatory agencies we visited, average approval times in some countries take longer than in the United States. These countries include Norway where the approval times range from 1 to 3 years, and Sweden where approvals averaged 27 months. However, in other countries the average approval time was from 7 to 12 months less than the 20 month average in the United States.

Because we did not have access to drug records of the foreign countries we were not able to determine why they approved drugs faster. However, there are a number of differences between the FDA and foreign drug approval processes.

But before I discuss these differences, I would like to talk about some of the factors that contribute to the slowness in the FDA drug approval process.

FACTORS CONTRIBUTING TO SLOWNESS IN DRUG APPROVAL PROCESS

To determine why many NDAs took so long to process, we interviewed industry and FDA officials including FDA reviewers, and analyzed the processing of the 132 original NDAs submitted to FDA for approval in calender year 1975. In addition, we analyzed the workload of FDA reviewers.

According to industry officials, the NDA approval process is hindered because:

--FDA guidelines are not precise and therefore are subject to varying interpretations.

--FDA changes reviewers during the NDA review which slows the process.

--Scientific and professional disagreements between FDA and industry are not readily resolved.

--FDA communications to industry are slow and there are long periods of time after submission of the NDA before the company is notified of any deficiencies.

On the basis of our analysis, industry appears also to have contributed to the slowness in processing NDAs by submitting incomplete NDAs and not giving high priority to correcting the deficiencies identified by FDA. Also, based on our analysis of FDA's workload, we found that it was unevenly distributed among reviewers which seems to further adversely impact on the approval timeframes.

Need clearer guidelines

According to industry officials, FDA guidelines are vague regarding the documentation to be submitted with an NDA.

As a result, industry officials believe FDA reviewers use personal preferences and standards that differ among reviewers. One industry official described the situation as "the target moving faster than the bullet."

Our analysis of NDAs submitted for FDA approval showed that NDAs are often returned to manufacturers for additional information. For example, 100, or 76 percent of the 132 NDAs submitted to FDA for approval in 1975 were returned to manufacturers one or more times for additional data. Most deficiencies related to chemistry and manufacturing control. In some cases, the correspondence between FDA and industry on such matters continued over a period of a year or more. Inasmuch as most NDAs failed to meet FDA requirements, it would appear that more specific guidance on the preparation and submission of NDAs would be helpful to manufacturers and would tend to speed up the process.

We contacted industry officials on 20 NDAs that had not been approved. Some of these officials cited FDA reviewers' inconsistency with regard to the amount of detail required with an NDA as a primary reason for deficiencies in the applications.

One industry official said that FDA reviewers require more detail today on chemistry and manufacturing controls than they did previously although the guidelines for the submission of such information have not changed since 1971.

FDA has recognized the need for improved guidelines and has stated that it plans to issue some of them later this year.

NDA reviewers change

In our discussions with drug industry officials, several pointed out that reviewers changed before the NDA processing was completed. This according to these officals has impacted on the time it has taken to review NDAs because the subsequent reviewer examined all the data that already had been reviewed, and raised additional questions on the data. Our analysis of 45 of the 132 NDAs showed that reviewers changed during the NDA processing in 17 cases. Furthermore, in 5 of the 17 cases the reviewers changed more than once.

We discussed reviewer changes with FDA officials. They explained that, generally, reviewers change when a reviewer leaves the agency or when the reviewer's workload necessitates a change to enable a more prompt review of pending NDAs.

Although some reviewer changes may be unavoidable, FDA should try to minimize such changes to reduce delays in approving NDAs.

Resolving scientific and professional disagreements

Industry officials told us that in some cases the issues raised by FDA involved areas of scientific

disagreement. They said there was no formal mechanism for prompt resolution of these disagreements. Presently, manufacturers can request administrative hearings to resolve such issues. This procedure is time consuming and is used infrequently. Industry officials did not provide specific examples of NDAs where such disagreements delayed the approval process and we were unable to clearly identify such examples because of the technical nature of the issues discussed in correspondence between FDA and industry.

With regard to scientific disagreements, pending bills (S.1045 and S. 1075), which are cited as the Drug Regulation Reform Act of 1979, provide for informal and expeditious procedures for review and, if possible, resolution of scientific disagreements. Such legislation, we believe, would provide a useful mechanism for more promptly dealing with scientific disagreements.

Communications between FDA and industry need improvement

Officials from the companies we talked with said slow or inadequate communications from FDA contributed to delays in reviewing and approving NDAs. In fact, 3 of the 8 companies considered communication problems as the primary reason for delays. Some officials indicated that reviewers did not provide manufactuers with timely feedback on deficiencies noted in their reviews.

FDA reviewers corroborated industry's perceptions. Twenty-one, or 46 percent, of the 46 reviewers we interviewed

said they did not notify manufacturers of NDA deficiencies until other members of the review team had completed their reviews. Medical officers, chemists and pharmacologists were consistent in this regard as 43 percent, 46 percent and 55 percent, respectively, said they did not notify drug companies until the other two reviewers finished their review.

We could not determine from FDA records we reviewed when the reviewers first notified the manufacturers of deficiencies in their NDAs. However, we noted instances where some reviewers completed their work 1 to 4 months earlier than others reviewers of the same NDA. In an attempt to reduce the review time for important drugs, FDA now requires each of its reviewers to reply to the manufacturer when their reviews are completed rather than waiting until all team members have completed their review.

INDUSTRY CONTRIBUTES TO DELAYS

We followed up with industry on 20 NDAs not approved as of June 30, 1978, some 30 months or more after the applications were initially submitted. Generally, they agreed with FDA's findings on these NDAs. However, the manufacturers generally placed a low priority on resolving these deficiencies because they determined that these drugs had a limited market.

Another reason, according to FDA officials, for NDAs taking a long time to process is because industry sometimes submits incomplete NDAs. Three of the 20 NDAs we followed up on were

incomplete according to FDA. These NDAs were for radiopharmaceutical drugs which were formerly regulated by the Atomic Energy Commission. This responsibility was transferred to FDA. Two of the radiopharmaceutical companies that sponsored these drugs told us the NDAs were incomplete because they had limited experience with FDA at the time they submitted the NDAs.

UNEVEN DISTRIBUTION OF WORKLOAD

Our analysis of FDA reviewers' workloads showed the workload varied widely, and this adversely impacted on the NDA review process. According to FDA officials, NDA review time could be shortened if workload could be more evenly shared by reviewers.

To gain insights on how workload is distributed within FDA, we analyzed the 1977 workload for 136, or 83 percent, of the 164 FDA drug reviewers. We concentrated our analysis on original NDA reviews because FDA officials cited them as the most complex and time consuming task for reviewers.

About 50 percent of the reviewers, which included medical officers, chemists, and pharmacologists, were responsible for reviewing most of the NDAs. Specifically, (1) fifty-one percent of the medical officers were assigned 88 percent of the NDAs; (2) forty-eight percent of the chemists were assigned 76 percent; (3) forty-nine percent of the pharmacologists were assigned 83 percent. This imbalance existed in most divisions. For example,

4 of the 8 medical officers in one division were assigned 20, or 87 percent, of the 23 NDAs in that division. In another division, 4 of the 8 chemists were assigned 28, or 82 percent, of the 34 NDAs. In a third division, 3 of the 6 pharmacologists were responsible for 53, or 88 percent, of the 60 NDAs.

In many cases, reviewers with heavy NDA workloads also carried a large load in other drug review work. For example, one of 8 reviewers in one division with 22 percent of the original NDA workload was also responsible for 25 percent of the supplemental NDAs and 16 percent of the applications for investigational new drugs in his division group.

In January and February 1979, we discussed our workload analysis with FDA division directors. They said workload imbalances exist because:

--some reviewers are more proficient than others and therefore are assigned a heavier workload, and

--some reviewers with a heavy workload were supervisors who were reluctant to delegate work to others.

Review proficiency seems to be a function of individual capabilities and experience. Division directors said some reviewers were chronic low producers and, for practicial reasons, are assigned fewer NDAs. In addition, less experienced reviewers are assigned fewer and less complex NDAs for review. To help the workload problem, division directors told us they are conducting

on-the-job training for less experienced reviewers and are counseling low producers to improve their performance.

We believe that effective on-the-job training and counseling for reviewers should permit FDA to distribute the workload more evenly. These measures, if effectively carried out, should help to improve FDA's drug review and approval process.

COMPARISON OF UNITED STATES DRUG APPROVAL SYSTEM WITH OTHER COUNTRIES' SYSTEMS

To obtain data on foreign drug approval systems, we visited nine countries and obtained the views of foreign regulatory and industry officials, medical experts, academicians and members of medical associations concerning the similarities and differences between their drug approval processes and those of the United States.

Some of the major differences relate to (1) use of expert committees, (2) post-marketing surveillance, (3) use of foreign test data to support safety and effectiveness of a drug, (4) flexibility in restricting the use of drugs, and (5) review of marketed drugs.

Expert Committees

FDA has a number of advisory committees not established by law who meet at irregular intervals and serve strictly in an advisory capacity. In contrast, most of the European countries we visited have established a committee of experts. In three of these countries Netherlands, Norway,

and Sweden the committee had been given the responsibility to make the decision to approve, reject or withdraw a drug. In the United Kingdom, its committee advises the government agency on the safety and efficacy of a drug; however, we were advised that its recommendations have always been followed.

The proposed Drug Regulation Reform Act of 1979 calls for the creation of advisory committees. Although this would legislatively mandate the existence of such committees in the drug approval process, their advisory capacity would remain unchanged.

The advantages we see to using expert committees as in European countries are that decisions are made by recognized experts in their fields whose decisions are more likely to receive wide acceptance. The use of expert committees would also appear to serve as a buffer to civil servants from outside influence and criticism.

Post-marketing surveillance

The objective of post-marketing surveillance is to monitor the use of a marketed drug to identify uncommon adverse reactions and to obtain more information on incidence of reactions already identified in clinical trials. In most countries we visited and in the United States, post-marketing surveillance consists of spontaneous reporting from physicians, hospitals, or manufacturers; and selected hospital monitoring. However, the United Kingdom, unlike most of the other countries, has a formal followup procedure

for adverse drug reaction reports and is able to protect the confidentiality of the reporting source. Because of this, according to a United Kingdom drug regulatory official, participation by physicians is greater in the United Kingdom than in other countries.

Further, this offical said that the post-marketing surveillance reporting system has a positive effect on the drug approval process because it gives the regulatory agency more confidence in being able to accept a lower number of clinical trials in the testing stages of new drug development.

The proposed Drug Regulation Reform Act will authorize FDA to require manufacturers to establish and maintain a post-marketing surveillance system.

Acceptance of foreign data

If a country were to accept adequate and well-controlled studies from another country without domestic verification, it could result in earlier introduction of a drug in that country. However, the acceptance of foreign data, and the extent of domestic verification of this data, varies from country to country. Some countries--Norway, Netherlands, Switzerland--may accept foreign test data without domestic verification, depending on its source. Other countries--United States, United Kingdom, and Sweden--will usually request domestic verification.

FDA's policy for acceptance of foreign data has not always been clearly understood. Officials from 4 of the 8 companies

we visited indicated that FDA would not accept foreign study data, and that safety and efficacy of a drug must be supported on the basis of duplicate domestic studies. FDA's Director of the Bureau of Drugs stated that FDA has had a reputation for not accepting foreign data for pivotal studies. However, the Deputy Director pointed out that since 1975 FDA's policy has been to place substantial weight on foreign studies as supporting evidence of a drug's safety and efficacy. In view of the misunderstanding of FDA's policy by some industry officials, we believe, FDA needs to clarify this policy.

United Kingdom has more flexibility

United Kingdom officials we interviewed indicated that their country is able to use more flexibility than the United States. We were advised, for example, that in approving a drug for marketing in the United Kingdom, the agency can restrict or limit the drug's use in a variety of ways. It may, for instance, limit the use of the drug to a hospital setting or restrict prescribing authority to certain types of medical specialists.

This flexibility, in our opinion, could enable the drug agency to authorize marketing of a drug which it might not otherwise be willing to approve without additional study.

Review of marketed drugs

The United Kingdom has appointed a panel of experts, the Medicines Commission, which periodically reviews marketed drugs to determine if it continues to be appropriate for those drugs to be on the market. The Commission reviews the country's experience with the drug and with any adverse side effects resulting from the use of that drug.

Thus, a drug, once licensed, does not necessarily remain on the market indefinitely without followup reviews. The United States does not follow a similar procedure.

USE OF COMPUTER TECHNOLOGY

We reviewed FDA's use of computer technology to assist reviewers in their NDA evaluations. FDA has access to 16 automated information systems containing information on (1) the review status and actions taken or pending on NDAs under review, (2) chemical structures of drugs already reviewed by FDA, (3) current and historical reports of adverse reactions to marketed drugs, and (4) scientific and medical articles on drugs.

Although some of these systems contain information that could facilitate the review and analysis of the large amount of data included with an NDA, most FDA reviewers we contacted are not using these systems. Few reviewers are aware of the automated information systems and what they contain. Reviewers told us they were aware of only 3 of the 16 systems. FDA has done little to increase reviewer awareness of computer support.

Also, reviewers generally did not participate in system design or development. Consequently, few automated systems support the drug review and approval process. Those that do, provide only marginal support. For example, one information system contains scientific information useful only to chemists. Animal or clinical test data useful to pharmacologists and medical officers are not available.

Because FDA's computer resources are not adequately used to support FDA reviewers, we believe FDA should

--evaluate the existing information systems to determine how they can better serve reviewers,

--make a survey of the needs of the reviewers that can be used in developing or redesigning information systems, and

--develop an education program for reviewers in the use of information systems.

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Mr. Chairmen, this concludes my statement. We will be glad to answer any questions.