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Address Presented

to

25th. Annual

Educational Conference

by

The Food and Drug Law Institute

in

Washington, D.C.

on

December 15-16, 1981

by

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"PROGRESS AND PROBLEMS IN FDA'S DRUG APPROVAL PROCESS"

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In May of last year the GAO issued a report on the FDA's drug approval process that followed almost 3 years of investigation of this procedure. This investigation included a considerable amount of time spent in talking with FDA staff and reviewing FDA files and procedures as well as in discussions with industry representatives. It also included time spent in endeavoring to determine the extent to which other countries' review process differed from that of the U.S.

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The report pointed out that while FDA has the responsibility, under the law, to assess both the benefits from use of drugs as well as the inherent risks in their use, there may well be procedures which could be adopted to reduce the length of time taken for this process to be completed.

Our analysis, at that time, showed that the average approval time for new drug applications submitted in 1975 was approximately 20 months. We further pointed out that several important drugs had been approved in certain foreign countries in less time than in the United States.

Our 1980 report went on to list some of the reasons for the delays, such as scientific and professional disagreement between FDA and

industry, imprecise FDA guidelines leading to varying interpretations, tardy FDA feedback to industry, lengthy chemistry reviews and industry's sometimes slow rate of resolving identified deficiencies. Other features which we cited as contributing to the slow approval time included congressional oversight, consumer involvement, the adversary relationship between industry and FDA and the latter's somewhat conservative approach to drug regulation.

GAO's analysis of new drugs submitted for FDA approval showed that 98 percent of the 132 NDAs submitted in 1975 were recycled by FDA for additional data. In some instances, recycling occurred as many as four times over a period of more than 3 years.

In its comparison of the drug review process in other countries, the GAO report discussed a variety of differences including post-marketing surveillance, the flexibility exhibited by foreign drug regulatory bodies, differences in the use of advisory committees, and variations in the degree to which foreign studies could be used as pivotal evidence of a drug's efficacy and safety.

It is of interest to note that GAO staff were told by drug regulatory officials of the United Kingdom that their confidence in post-marketing

surveillance is one factor that permits them to approve drugs more quickly. The report points out that although there are six times as many physicians and dentists in the United States than in the United Kingdom, the number of adverse drug reaction reports being submitted to the official agencies is about the same.

The General Accounting Office study indicated that in Europe the decision making process for drug approval is generally shared by a committee of experts, whereas in the United States, FDA assumes full responsibility for the decision and tends to require more documentation than do these expert committees in arriving at a decision.

Following issuance of this report, the General Accounting Office began a study of FDA's efforts to speed up the drug review process. We compared processing time of drug applications received in FY 1979 and 1980 with those received in FY 1976 and 1977. This comparison was based on a comparable time period. Our analysis showed that FDA had decreased its processing time of important drugs by 5.7 months or 36% since October 1978; this represents a considerable improvement. However, the study ascertained that only two of FDA's six reviewing divisions had actually reduced their

review time; the other four divisions actually showed an increase in review time.

It was also noted that although FDA's efforts to speed up the drug review process have achieved some success, many of the obstacles which prevent timely review and approval have not been removed. The General Accounting Office specifically examined six initiatives undertaken by FDA to reduce drug review time. These are the steps which the Food and Drug Administration considers to be among the most important. They include efforts to improve communication with industry by conducting conferences at the end of Phase II clinical testing; an invitation to sponsors of important drugs to submit manufacturing and controls information before the NDA is fully prepared; a priority review system to expedite processing of important new drug applications; efforts to speed up the procedure for validating the sponsor's methods to test a drug's identity, quality, strength and purity, and efforts to improve the timeliness of the work performed by the Divisions of Biometrics and Biopharmaceutics.

As a result of contacts with some 30 drug firms, it seems evident that they strongly support end of Phase II conferences, and indeed, those who have participated in the conferences characterized them as excellent and helpful.

On the other hand, while early submission of manufacturing and controls data appears to have some potential to help speed up drug review, few firms appear to be submitting that data, often because they do not make final decisions on dosage forms until they are almost ready to submit the NDA.

The priority review system is intended to give important drugs special attention so that their applications are handled more rapidly. However, GAO found that the Food and Drug Administration has not defined this policy in writing and many reviewers did not understand how the policy is to be implemented. Therefore, while some reviewers give important drugs high priority, others do not and continue to treat all NDAs on a first-come, first-served basis.

GAO also found that in spite of FDA's efforts to speed up the validation of analytical methods proposed by drug firms, this may well be, on occasion, the sole factor delaying NDA approval. For example, our analysis of 14 important new drug applications submitted for review in 1979 and 1980 showed that methods validation averaged 182 days for these drugs. FDA has recognized the need to clarify its methods validation requirements and, in March of this year, established a task force to address this issue.

Finally, much remains to be done to expedite processing by the Divisions of Biometrics and Biopharmaceutics.

As early as March 1978, the Commissioner of FDA indicated the Agency's intention to rewrite its regulations on INDs and NDAs. However, a draft of these regulations is not yet available for public comment and is not expected to be published until sometime next year; furthermore, it is not anticipated that they will become final for at least 2 more years.

On the basis of interviews with a number of officials from the Bureau of Drugs, it would appear that several of the changes being considered for incorporation in these revised regulations should help improve the efficiency of the drug review process. These include increased use of post-marketing surveillance as a condition for new drug approval, eliminating the requirement that companies submit detailed individual case reports with each new drug application, allowing manufacturers more opportunity to voluntarily withdraw previously approved NDAs without fear that vital data would be disclosed to competitors, decreasing the number of supplements to be filed by industry and reviewed by FDA and tailoring applications to FDA's different review units as well as securing improved coordination among these review units.

In addition, the Food and Drug Administration's willingness to accept foreign studies seems to be increasing, although the extent to which this is likely to supplant domestic verification appears somewhat unclear and uncertain.

To turn for a few moments to a consideration of orphan drugs, I might point out that the General Accounting Office, earlier this year, transmitted a letter to the Chairman, Subcommittee on Health and the Environment of the House Committee on Energy and Commerce reporting on a review it had undertaken of the Federal Government's involvement in drug development programs. This report noted that, in fiscal year 1980, the Federal Government was directly involved in the development of some 35 so-called orphan drugs at a cost of $79.6 million. Almost all of this activity was housed in the National Institutes of Health, with the greatest portion being located in the National Cancer Institute; the latter Institute had responsibility for the development of 21 of these drugs. In addition to cancer chemotherapy, other orphan drug categories in which the Federal Government is involved include contraceptives, epilepsy, vaccines, malaria and tropical diseases.

The primary reason for Federal involvement in research and development of these drugs is, of course, the perceived need for attention to a specific

disease or problem in cases where industry might not be reasonably expected to contribute. This is because of the uncertain profitability of developing and marketing these new drugs, as indicated by the probable size of the market in relation to developing and marketing costs.

The National Cancer Institute's program actually began in 1955 with a Congressional appropriation of $5 million, prompted mainly by the discovery that nitrogen mustard and methotrexate appeared to be quite useful in the treatment of leukemia and some lymphomas. Also, according to a 1957 National Cancer Institute report to the Congress, industry activity in anti-cancer drug development had been intermittent because most firms considered anti-cancer drug development to be a risky, low-return investment, testing methods were slow, expensive and uncertain,and clinical trials were difficult to conduct. Finally, industry felt that new anti-cancer drugs might well be considered to be in the public domain, and this would limit the opportunity to recover costs or make a profit.

In most instances, the National Institutes of Health identify and acquire new drugs by maintaining contact with scientists in industry and research institutions, reviewing research literature, synthesizing existing drugs or

experimenting with natural products. To encourage industry to submit chemicals for its drug development program, the National Cancer Institute adopted a policy in 1956 under which suppliers of patented chemicals were allowed to retain their patent rights and to acquire exclusive rights to data developed under the program; suppliers of unpatented drugs were given exclusive rights to the developed data.

Alltogether, under these various orphan drug programs, a total of more than 600,000 chemical compounds have been acquired for screening. The screening process includes testing in animals or in the laboratory, followed, as appropriate, by further pre-clinical studies as prescribed by FDA regulations.

Following revision of its practices in 1975, the National Cancer Institute now exposes some 15,000 chemical compounds per year to a preliminary screen against a single type of tumor in mice. Of this number, less than 500 are usually shown to be active and it is this group that is subjected to further testing.

Clearly, the degree of involvement by the Federal Government depends on the extent to which private industry is willing to participate. In most instances, however, Federal involvement in securing approval of a new drug

ends when clinical studies are completed. In most instances, the evidence obtained in the screening and in pre-clinical and clinical studies is turned over to industry for use in applying for and securing an approved NDA from the Food and Drug Administration.

Since their inception, these Federal drug development programs have resulted in some 400 drugs entering clinical trials under an IND; as previously indicated, a total of 35 new drugs have been developed. Currently, 102 drugs are still being studied under approved INDs or are being considered by the Food and Drug Administration for NDA approval. About 70% of this number are anti-cancer drugs.

The 17 year patent term has remained unchanged in this country since 1861. It represents, of course, a judgement as to a desirable length of time to permit the public to benefit from the innovations that can be stimulated by granting exclusive rights to the inventor. No one can prove that 17 years should be considered the perfect time period. However, it is clear that, in the case of drug innovation, the period of exclusive marketability is currently much less than 17 years and indeed is often closer to 7 years. This is partly because final FDA approval may take several years. This matter takes on added

significance when one considers that it now costs an average of $70 million for each new drug entering the market place. Thus, the incentives to invest in pharmacological research and development are somewhat less than would be true if 17 years of exclusive marketing were to apply. This lengthy time taken for drug approval is a fairly recent occurrence. Twenty years ago, the process took about 2 years as compared to between 7 and 10 years today. Clearly the emphasis on ensuring safety and efficacy, important as it may be, has taken its toll.

GAO's position on this issue was summed up in a letter addressed to the Chairman, Senate Judiciary Committee earlier this year. In that transmittal, we expressed the view that increases in patent term should have a positive impact on both monetary return and internally generated cash flow for the pharmaceutical industry. We suggested that this, in turn, would undoubtedly stimulate research and development and eventually result in an increase in new drug innovation.

We further reasoned that we would expect that the patent protection term would become an increasingly important economic incentive influencing research and development decisions in the future. "Breakthrough" type drugs would

have a particular propensity for being positively affected by patent restoration since they tend to have above average risk but longer expected product life through obsolescence.

It was also our opinion that patent restoration would have a significant affect on new drug prices because of the fact that those drugs would be able to maintain an exclusive market for longer periods of time. Hence, the savings that consumers obtain through price competition would likely be deferred. Accordingly, it was our judgement that, on balance, consumers would benefit financially to the extent that the gains on innovation stimulated by patent restoration exceeded the increased costs from higher drug prices. This, of course, is in addition to the possible gains in relief of human suffering which result from increased drug innovation.

As already indicated, the past several years have seen the General Accounting Office engaged in a fairly intensive review of FDA's drug approval process. Growing out of this effort, ladies and gentlemen, I would like to conclude my remarks by suggesting several issues which, in my judgement, might well be addressed in an effort to speed up this country's drug review and approval process.

1. The relationship between FDA and the drug companies. This relationship has been and continues to be an adversarial one; it is clear that the more cooperative relationship that exists in many other countries has proved conducive to a better rapport and in turn, quite possibly, to a more speedy review process.

2. The degree to which FDA is willing to accept foreign studies without the necessity of having to carry out domestic pivotal studies. This is not to deny that some domestic verification may, in some instances, be required. Much, however, depends on the nature and extent of the domestic studies required to be performed. Pivotal studies often tend to be time consuming and expensive.

3. Whether or not FDA would be willing to permit the drug companies to retain patient records rather than submit them to FDA with the application. While the submission of detailed patient records does not necessarily mandate that they be reviewed, there is clearly a tendency, in some instances, for this to occur. It seems to me that summary information submitted with the application should be sufficient, supported by detailed patient data which could be retained by the applicant, to be made available if needed.

4. The advisory committee structure in FDA might well be examined in comparison to the systems used in a number of other countries. Certainly, there are major statutory differences, including those dealing with conflict of interest. However, the fact remains that the advisory committee structure in many European countries appears to lead to a much stronger participation and influence on the part of the Nation's pharmacological experts in the drug review and approval process than seems true in this country; this, in turn, seems to create a more favorable climate within the medical community.

5. Changes in FDA's classification system with a view to ensuring that really important drugs receive first priority. FDA's current system for classifying drugs does not appear to distinguish between those drugs which one might consider life saving or highly important for a large number of people as compared to breakthrough drugs which might have a limited effect or might be useful to relatively few persons. These different categories currently appear to be considered equally important; therefore, to the extent to which they are placed on a fast track, they seem to be accorded similar treatment.

6. The possible increased use of part-time physicians by FDA with those physicians spending part of their responsibilities outside of FDA in clinical

work or research. This could reduce the attitude outside of Government that FDA's physicians are too far removed from day-to-day clinical activity and cannot, therefore, remain in touch with the field.

7. Increased flexibility in FDA operations which would include, for example, the ability to restrict the marketing of drugs so that they might be available for use only within a hospital setting or by certain specialists or under other certain restricted conditions rather than to always be generally available. This should have the effect of making it easier to place drugs on the market at an earlier date.

8. Improvements in post-marketing surveillance. Admittedly this is a complex question and not an easy one to solve; however, increased ease of reporting, together with some relief from the fear of malpractice suits, accompanied by feedback of useful information to physicians might well increase physician participation.

9. Routine review of marketed drugs with the objective of removing from the market those drugs found to be unsafe or ineffective. If a time limit were placed on the length of time during which a drug would be automatically allowed to be marketed following which a review would be required to ascertain its status, more rapid initial approval might be possible.