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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Drug Testing

SUMMARY AND ANALYSIS

SELECT COMMITTEE ON SMALL BUSINESS
UNITED STATES SENATE

Prepared by the

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A SUMMARY ANALYSIS AND DISCUSSION OF ISSUES HIGHLIGHTED DURING THE 1968 AND 1969 HEARINGS ON DRUG TESTING, WITH A REVIEW OF MORE RECENT FINDINGS AND GOVERNMENT ACTIONS RELATING TO FDA TESTING REQUIREMENTS

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LETTER OF SUBMITTAL

September 12, 1979

Honorable Gaylord Nelson
Chairman, Select Committee on Small Business
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am pleased to submit this analysis and review of the drug testing hearings that were conducted before the Subcommittee on Monopoly in 1968 and 1969. This summary report, prepared at your request, is particularly timely in light of certain testing provisions of the proposed Drug Regulatory Reform Act, currently being considered by the 96th Congress.

The hearings summary was prepared by Ms. Janet E. Lemke, a private consultant, under Congressional Research Service contract (CRS 79-75-1). It was reviewed and edited by Ms. Vikki Zegel, Analyst in Life Sciences, of the CRS Science Policy Research Division. The report provides an analytical review of the issues raised during the 1968 and 1969 hearings, background information on FDA drug testing requirements, a brief history of drug regulatory legislation, and an update of the drug testing issues highlighted in the earlier hearings.

May I express my appreciation for this opportunity, on the part of the Congressional Research Service, to cooperate with your committee in the preparation of this timely and most useful report.

Sincerely,

Gilbert Gude
Director

C O N T E N T S

PAGE

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Drug Testing

I. INTRODUCTION

A. Purpose

The purpose of this report is three-fold: (1) to review the major issues raised during the subcommittee's hearings in 1968 and 1969 regarding the testing and evaluation of new drugs 1/; (2) to examine these and related issues in light of recent events, current information, and new procedures; and (3) to discuss Federal Government actions relating to drug testing issues.

B. Background

In the late 1960s, the Senate Subcommittee on Monopoly was receiving the first testimony in what was to become a continuing series of hearings on competitive problems in the drug industry. In 1968 and 1969, drug testing was targeted as a separate and distinct issue. Although the testing of drugs inevitably was addressed during discussions of individual drug

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1/ U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Competitive Problems in the Drug Industry. Hearings, 90th Congress, 1st Session; Vol. 10. Hearings held December 11, 17, 18, and 19, 1968, and January 23, 1969. Washington, U.S. Govt. Print. Off., 1969 (pages 3911-4296). [Hereinafter included in reference to The 1968-1969 Hearings on Drug Testing.]

--- Competitive Problems in the Drug Industry. Hearings, 91st Congress, 1st Session on MEDICAL STUDENTS-AMA-FDA (DRUG TESTING); Vol. 14. Hearings held June 19, August 7 and 12, 1969. Washington, U.S. Govt. Print. Off., 1969 (pages 5479-5919). [Hereinafter included in reference to The 1968-1969 Hearings on Drug Testing.]

issues, it was more extensively examined by three witnesses in their discussion of drug testing procedures and standards. 2/

The subcommittee's concern in this area was expressed by its chairman, Senator Gaylord Nelson in his opening remarks on August 12, 1969:

> The dangers involved in the dependence on drug firms to perform, finance, direct, and arrange for the testing of drugs in which they have a commercial interest is obvious. Drug firms are anxious, of course, to get new drugs on the market and to increase their sales. There is thus an inevitable tendency, no matter how conscientious the firm, to emphasize the positive features and deemphasize the negative. Many of the people they engage to do their testing are equally anxious to secure additional contracts for drug testing. FDA has found that the accuracy and objectivity of some of these drug testers leave much to be desired. 3/

The problems associated with clinical trials, however, go beyond potential bias alone; scientific, regulatory, ethical, legal, and financial concerns are all involved. Groups participating in, or affected by, the issue of drug testing include the pharmaceutical industry, the Food and Drug Administration (FDA), the medical profession, and the consumer. The drug industry is responsible for the development and marketing of drugs. The FDA is responsible for assuring that the drugs destined for market are safe and effective. The medical profession and the public rely on the scientific quality and ethical standards employed by the drug manufacturers and FDA in the development and approval of new drugs.

2/ Drs. Herbert L. Ley, Jr., Franz J. Ingelfinger, and Paul Lowinger

3/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5641.

To assure that the drug development system operates smoothly and properly, regulatory requirements have been imposed by the Federal Government for the ultimate purpose of protecting the public from substandard or dangerous drugs.

The process of new drug development involves two stages of FDA approval. The first stage is when a drug sponsor has determined through basic laboratory and animal studies that a drug might have applicability to humans. In an Investigational New Drug application [IND] to FDA, the drug sponsor is seeking approval to use the drug in clinical tests involving humans. After the clinical trials, if the drug has been successful and has shown "safety" and "effectiveness," the sponsor then submits to FDA a New Drug Application [NDA]. FDA's approval of an NDA means that the drug firm may begin marketing the drug.

In spite of restrictions and cautions on the part of FDA in approving new drugs, a tremendous number of pharmaceuticals has flooded the market in the past forty years:

> . . . Since 1938, nearly 1,000 new individual drug entities have been approved for marketing in the U.S. Physicians and patients today confront a bewildering array of more than 100,000 Rx drug products, and as many as 250,000 over-the-counter formulations...In short, fully 90% of all Rx drug sales today involve drugs that have come on the market since 1938. 4/

4/ HEW Secretary Califano Proposes Major Changes in Nation's Rx Drug Laws (Text of a speech...). The Blue Sheet (Supplement), vol. 20, October 12, 1977: S-2.

Each of these drugs was approved for market by FDA. The approval of drugs inevitably becomes part of any discussion on drug testing, since it is the tests and their results which form the basis upon which a drug is approved or disapproved.

In 1978, FDA approved 86 new drugs for market. Of these, 23 were classified as new molecular entities; that is, the active basis of the product had never before been marketed in the U.S. Of the 23, five were considered to offer important therapeutic gain over existing products, nine offered modest therapeutic gain, and nine offered little or no therapeutic gain. 5/

As of May 31, 1979, FDA had calculated that there were 1,816 active INDs [investigational new drug applications]. Thirty-nine represented important therapeutic gain; 157 offered modest therapeutic gain; and 1,589 offered little or no therapeutic gain. Of the total, 722 were new molecular entities, 102 of which offered important or modest therapeutic gain. 6/ The remaining 1,094 INDs represent new combinations or formulations of older drugs, new derivatives, drugs already marketed by other firms ("me-too" drugs), or drugs already marketed but now being tested for other purposes.

5/ Kennedy, Donald. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology. Hearings, 96th Congress, 1st Session. Hearings held on June 21, 1979: unpublished, [Appendix C, Table 1 of his statement].

6/ Ibid., [Appendix C, Table 4 of his statement].

Clinical trials necessitate the use of humans to test the drug's pharmacologic actions in the body. It was recently estimated that more than two million Americans are now involved in clinical trials. 7/ The ethical implications of using humans for experimentation purposes is a major issue in drug testing. This subject was discussed in the 1968-1969 hearings on drug testing and has become a major issue in itself during the 1970s.

From the time of the 1968-1969 hearings to the present legislative proposals, terminology has posed problems. Current standards require that new drugs be "safe" and "effective." While this is easy to legislate, it is difficult to enforce. For the sake of clarity, several terms are defined below:

A drug is 1) any article recognized in official drug compendia; 2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; and 3) articles intended to affect the structure or any function of the body. A "drug" is differentiated from a "device" in that a device does not achieve any of its principal intended purposes through chemical action within or on the body and which is not dependent upon being metabolized [broken down

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7/ Who Shall Live? The Tribulations of Clinical Trials. American Pharmacy, vol. NS19, May 1979: 234.

or chemically altered in the body] for the achievement of any of its principal intended purposes. 8/

Effective means that the drug has the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. 9/ A product's effectiveness simply indicates that it meets its professed claims, -- possibly only as well as, or less well than, a product already on the market.

"Me-too" drugs are products identical to drugs already on the market, but manufactured by a different firm after the original patent has expired.

New molecular entities [or new drug entities] represent original and unique drugs. Such products are new in that their basic component has never before been marketed in the U.S.

Safety, with regard to pharmaceuticals, has not been defined in the law, although the Food, Drug, and Cosmetic Act does require that investigations "show whether or not such drug is safe for use..." 10/ Since it is difficult, if not impossible, to declare any drug completely safe and free of risks, a recent legislative proposal (96th Congress, S. 1075) attempts to define

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8/ The Federal Food, Drug, and Cosmetic Act, As Amended. January 1979. Chapter II, sec. 201[321](g)(1); (h)(3).

9/ Ibid., Chapter V, sec. 505[355](d)(5).

10/ Ibid., Chapter V, sec. 505[355](b)(1).

"safe" to mean that the health benefits of the drug outweigh the health risks presented by the drug. 11/

Substantial evidence means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved..." 12/*

The testimony at the 1968-1969 hearings relating to drug testing focused on the problems which plagued the system. Witnesses and subcommittee members seemed to agree that improvements needed to be made, but suggestions as to how the deficiencies could best be corrected were varied. A significant portion of the testimony revealed that the Drug Amendments of 1962 posed problems for the drug industry by adding "effectiveness" as a standard that all new drugs must meet. Until that time, manufacturers were only

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11/ 96th Congress, S. 1075, introduced May 3, 1979 by Senator Edward Kennedy. The bill was amended and favorably reported by the Committee on Labor and Human Resources September 18, 1979; it was further amended and passed by the Senate on September 26, 1979.

12/ Federal Food, Drug, and Cosmetic Act, as Amended. January 1979. Chapter V, sec. 505[355](d)(6).

* "Substantial evidence" became an issue in Senator Gaylord Nelson's drug hearings in 1968 during discussions on the drug indomethacin. FDA approved this product based on studies which were subsequently questioned as to whether or not they actually constituted "adequate and well-controlled" investigations showing the drug's efficacy. The hearings on indomethacin are found in parts 7 and 8 of the Subcommittee on Monopoly's hearings on Competitive Problems in the Drug Industry (90th Congress, 2nd Session. Hearings held on May 2, 3, and September 17, 1968.)

required to prove that a drug was "safe." The efficacy requirement entailed increased testing on the part of the drug sponsor. This contributed to longer drug development and approval time.

The 1962 Amendments represent the last piece of enacted legislation on drug regulation to date. Since the implementation of that Act, much criticism has been leveled at the drug regulatory system. Recognizing the need for revision of the law, Congress has held extensive hearings, delving into the deficiencies of the existing system and examining the arguments of the drug industry, the Food and Drug Administration, the medical profession, and the public consumer. Evolving from these investigations is legislation known as the "Drug Regulation Reform Act of 1979", presently under consideration in the 96th Congress. This bill, S. 1075, addresses the many issues of the drug regulation controversy. Many of these issues bear directly or indirectly on the testing and approval of new drugs. The provisions attempt to close gaps and tighten the existing system, while at the same time, they are designed to accommodate the needs of the pharmaceutical industry. One of the major charges today is that increased Federal regulations have stifled drug innovation and resulted in increased and unreasonable delays in drug approval. The ultimate goal of current efforts, then, is to correct deficiencies in the system and expedite the availability of promising new drugs, without compromising the necessary, high standards of safety and efficacy.

C. Policy Issues

During the 1968-1969 hearings, drug testing as a specific and singular topic was examined on a somewhat limited basis. On the other hand, it was an inevitable part of most discussions on individual drugs, such as the oral hypoglycemic drugs, indomethacin, chloramphenicol, and so on. Where it was discussed, however, as a separate and distinct subject, several issues emerged as being crucial and problematic in the drug testing system.

The process of selection of an investigator to conduct the drug trials was considered to be deficient in several respects. The availability of trained investigators, the qualifications of the investigators, and the financial and obligatory relationship of the drug firms to the investigator were questioned. The potential for bias, both in the selection of the investigator and in the investigator's attitude toward his sponsored work, was a prominent feature in the testimony.

Instances of substandard testing due to inadequacy or negligence were examined, and the occurrence of poor quality work was generally believed to cast doubt on the reliability of the resultant data. Furthermore, false, fraudulent, or misleading data was a major issue in the 1968-1969 hearings. FDA, which depends on data submitted by the drug firms to make its decisions on new drug approval, found that the information it received was not always reliable. Occasionally, pertinent test results were omitted from the submissions--for example, results which indicated adverse reactions. FDA also found that data was, on occasion, manipulated in some way to distort

53-690 O - 79 - 2

the original findings. In general, witnesses and subcommittee members questioned the ability of the drug firms to maintain quality control over themselves.

All of the witnesses and contributors to these hearings discussed their views on the development of an independent, third party source, which would either conduct the tests, select the drug investigators, and/or perform an oversight function. Implementation of such a concept would take the responsibility for the trials out of the hands of the drug firms, thereby reducing the potential for bias, and it would streamline the overburdened system at FDA as it existed then.

The use of human subjects in drug trials raised serious questions at the hearings. In general, it was felt by witnesses that abuses of human subjects, particularly prisoners, would be less likely to occur if a structured oversight body was in operation. During the 1970s, steps were taken to further ensure the rights and protection of human test subjects.

Except for human subjects, the issues identified in the 1968-1969 hearings have become somewhat overshadowed by other drug issues, although they remain critical factors in the drug process. Literature and recent congressional hearings have shown that the loudest protest today is over delayed approval of new drugs in this country. Regulatory requirements in drug development and approval have become an impediment to drug progress, according to many critics of the present system. Internal FDA procedures and organization have been identified as being deficient in many areas, and in need of revision. It has become clear that changes are necessary.

To this end, current legislative proposals would overhaul existing drug law; they would act on deficiencies in the drug development and approval process; they would create a separate drug center; and they would enhance the authority of FDA. It is entirely possible that by the end of 1979 or 1980, legislation will be enacted which will significantly change drug regulatory policy in the United States. The struggle at this point is over meeting the needs of the various parties involved, without sacrificing standards of quality.

II. FDA AND THE DRUG APPROVAL PROCESS

A. The Drug Development and Approval Process

The first step in the development of a new prescription drug is the discovery of possible therapeutic effects. If a chemical shows this potential, the manufacturer subjects it to screening tests and studies in animals. At this basic stage it is determined if drug effects are present. If so, the additional tests determine dosage ranges, toxicity levels, and the possibility of safe application to humans.

If the sponsor believes the drug may have human application, the next step is to test the product in humans. Before proceeding to these clinical trials, the sponsor must submit to FDA a "Notice of Claimed Investigational Exemption for a New Drug," commonly known as an IND or investigational new drug application. This application describes in detail the plan for the proposed investigation, including: the nature of the proposed trials, identification of the investigators and their qualifications, available facilities, results of preclinical tests from animal and laboratory studies, a description of the drug and how it is manufactured and controlled to meet standards, and what data will be transmitted to the investigatiors. 13/ Agreement to report any adverse effects, to obtain consent from test subjects, and to submit progress

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13/ U.S. Congress. Senate. Committee on Labor and Public Welfare, Subcommittee on Health; and Committee on the Judiciary, Subcommittee on Administrative Practice and Procedure. Preclinical and Clinical Testing by the Pharmaceutical Industry, 1975, Part I. Joint Hearings, 94th Congress, 1st Session, on the Examination of the Process of Drug Testing and the FDA's Role in the Regulation and Conditions Under Which Such Testing is Carried Out. Hearings held July 10 and 11, 1975. Washington, U.S. Govt. Pring. Off., 1975, p. 108. [Hereinafter included in reference to The 1975-1978 Hearings on Drug Testing.]

reports, are made in the IND. The test results in the IND should demonstrate to FDA that adequate testing has shown promise for use in humans, and that test subjects will not be exposed to unreasonable risk.

Upon approval of the IND by FDA, the manufacturer may proceed with clinical testing in humans. This testing is roughly divided into three phases:

> In Phase 1, healthy volunteers are generally used for the first drug trials, to determine the chemical actions of the drug. Short-term tolerance, metabolism, absorption, excretion, dose ranges, and methods of administration (oral or injected, for example) are studied. If Phase 1 studies are safely completed, Phase 2 is initiated in a limited number of patients having the disease or condition for which the drug is intended.
>
> At Phase 2, the investigator begins to ascertain the effectiveness of the drug. Both of these first phases are carried out using a small number of test subjects. If Phase 2 indicates efficacy and if long-term animal tests still show the drug to be safe, then Phase 3 studies are begun.
>
> Phase 3 is the full-scale clinical trial stage, using many more patients. The drug's safety and efficacy are further examined, and optimal dosages are determined.

FDA reserves the right to terminate an IND, or part of it, for any of the following reasons: 14/

-- if it contains false data;

-- if continuing the tests would be unsafe;

-- if the IND plan is not being followed;

14/ The 1975-1978 Hearings on Drug Testing, Part I, pp. 110-111.

-- if the drug is shown to be unsafe or ineffective;

-- if manufacturing facilities and controls are inadequate;

-- if the investigational plan is unreasonable;

-- if the product is being improperly commercialized;

-- if data supplied to investigators is incomplete;

-- if records are not kept and reports not made; or,

-- if adverse effects are not reported to FDA.

FDA also requires that clinical testing conducted on institutionalized subjects be carefully monitored by institutional review committees.

After successful completion of the clinical trials, the sponsor applies to FDA for approval to market the drug. This New Drug Application, known simply as an NDA, must include the following information: full reports of investigations showing safety and efficacy; the components and composition of the drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of the drug; samples of the drug; and specimens of the proposed labeling of the drug. Upon receiving the NDA, the appropriate division in FDA's Bureau of Drugs reviews the application to determine if it is complete and whether the benefits of the drug outweigh the risks. FDA may require that further studies be conducted before approval can be given, or it may determine that the benefits do not outweigh the risks. Once an NDA is approved, however, the drug sponsor may begin marketing

the drug. Any subsequent amendments to an approved drug's NDA must be reported to FDA and approved. Approval of an NDA can be withdrawn by FDA if the Agency subsequently finds that the drug shows "imminent hazard" to the public. 15/ FDA can also require label changes and warnings to be issued if subsequent information on the drug shows this to be necessary. Periodic reporting is required by FDA -- during the first year, a report is to be submitted every three months; during the second year, a report is required every six months; and an annual report is required each year thereafter. 16/

B. FDA Policies, Procedures, and Regulations

Within FDA's Bureau of Drugs there are six drug classification divisions: cardiopulmonary/renal, neuropharmacological, metabolic/endocrine, anti-infective, oncology/radiopharmaceutical, and surgical/dental. Incoming new drug applications are referred to the appropriate divisions for review. In addition, FDA began rating newly approved drugs in 1974-1975, according to a double classification system (see appendices). The first element is numerical (1 through 6) and evaluates the drug's newness or uniqueness. "1" means the product is a new molecular entity marketed for the first time in the United States, while a "5" is a "me-too" drug.* The second

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15/ The Federal Food, Drug, and Cosmetic Act, Chapter V, sec. 505[355](e).

16/ Youngs, Maynard L. Marketing a New Drug Product. Food Drug Cosmetic Law Journal, vol. 33, November 1978: 639.

* A "me-too" drug is a product identical to one already on the market. but made by a different pharmaceutical manufacturer.

element is a letter (A, B, or C) and indicates the drug's therapeutic value. "A" indicates a "breakthrough" drug, showing important therapeutic gain over existing drugs; "B" indicates a modest therapeutic gain; and a "C" rating indicates little or no therapeutic gain. At the time of the writing of a report which appeared in the October 1978 issue of Consumer Reports, FDA had rated 220 products, not all of which were prescription drugs. Nearly one-half of all the products were rated "5-C" -- "me-too" drugs with little or no therapeutic gain. The Consumers Union interpreted a "5-C" rating to mean "profit, but certainly not progress." 17/ It should be noted, however, that such a product may on occasion offer an alternative (perhaps safer or more beneficial) choice of treatment for a particular patient. This rating system is not made routinely available to the medical profession.

In testimony before the House Subcommittee on Science, Research, and Technology on June 21, 1979, FDA Commissioner Donald Kennedy commented on this classification system saying that this system "has proved useful in assessing historical trends in drug availability and in considering how to deploy FDA resources to facilitate evaluation of important new drugs and minimize the time required to review NDA's for these new entities." 18/ He went on to say that one benefit of the system was that

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17/ How the FDA Rates Prescription Drugs. Consumer Reports, vol. 43, October 1978: 578.

18/ Kennedy, Donald. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology, (unpublished), June 21, 1979: 14.

it provided a sound method of evaluating both the drug innovation in the industry and the efficiency of the FDA approval process.

The FDA policy on accepting foreign data has been a subject of much debate in recent years. Drug industry representatives have repeatedly protested the fact that FDA would not accept foreign data when widespread usage of a drug in foreign countries had already established clinical parameters. In 1973, criteria were proposed which would allow the acceptance of foreign data. A 1977 report claimed, however, that such data could only be supplementary in nature and that primary data had to be generated in the United States. 19/ Testimony by James Ferrendelli on June 19, 1979, concerned the acceptance of foreign data in the approval of valproic acid for the control of epilepsy. 20/ FDA requires the submission of at least two adequate and well-controlled investigations demonstrating substantial clinical evidence of safety and efficacy. FDA eventually approved valproic acid, taking into consideration foreign studies on the drug. Commissioner Kennedy, in an effort to "set the record straight," emphasized in 1979 that FDA does have a policy of fully accepting foreign studies when such studies meet the same standards of quality required in this country. 21/ In 1975, FDA published regulations to that effect,

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19/ Parker, J.E.S. Regulating Pharmaceutical Innovation: An Economist's View. Food Drug Cosmetic Law Journal, vol. 32, April 1977: 173.

20/ Ferrendelli, James. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology, (unpublished). June 19, 1979.

21/ Testimony of Donald Kennedy, June 21, 1979, p. 21.

also stating that "these trials must be conducted according to the ethical standards of the Declaration of Helsinki or of the laws of the country of origin, whichever provides the greater protection to human participants." 22/ In order to assure that a drug will be safe and effective under the exact conditions of use in this country, FDA usually requires that one of the critical studies on a new drug be conducted in the U.S.

Other FDA policies, procedures, and regulations relating directly or indirectly to drug testing and approval are discussed more fully in other sections of this report.

C. New Drug Approval Time

The drug regulatory issue of most concern in the 1970s seems to be the length of time it takes to have new drugs approved for marketing by FDA. The basic argument on the part of the drug industry is that increased Federal regulations on drug testing and development and long approval times have stifled drug innovation, raised the costs of development, and prevented patients from receiving benefit from promising new drugs. Because of these delays, the industry claims the United States is being left behind other countries in pharmaceutical progress. The Government counters with the argument that the U.S. drug regulatory system operates in the best interest of the public by assuring that marketed drugs are safe and effective. What everyone would like to see, therefore, is the expeditious approval of

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22/ Testimony of Donald Kennedy, June 21, 1979, p. 21.

promising new drugs, without compromising the quality controls on safety and efficacy.

The infamous thalidomide case is perhaps the most dramatic example in support of the lengthy approval process in this country. While this product was being marketed in other countries, FDA withheld its approval because of suspicions of inadequate test data to support claims of safety, and questioning letters and reports appearing in countries where the drug was available. Approval of the NDA for thalidomide was held off by FDA for more than two years before the relationship between the drug and birth deformities was realized.

To conclusively resolve the time delay dilemma, one would need to know the cost in terms of morbidity and mortality due to deprivation of better drugs over a period of time, compared to the costs of unanticipated side-effects and occasional drug tragedies if drugs are marketed sooner. There is no way to do this kind of balancing with unforeseen events. In 1973, Sam Peltzman, an oft-quoted economic analyst, published a study of the 1962 Drug Amendments. He weighed the costs of compliance with the efficacy requirements against the waste of ineffective drugs on the market, and concluded that "benefits foregone on effective new drugs exceed greatly the waste avoided on ineffective drugs." 23/

23/ Peltzman, Sam. An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments. Journal of Political Economy, vol. 81, September/October 1973: 1049.

Critics of the delay in introducing drugs into the U.S. attribute the protraction to several causes, but most often to increasing regulatory requirements, and in particular the efficacy standard required by the 1962 Act. Dr. Louis Lasagna, another outspoken critic, claims that one source of delay is FDA's demand that at least two tests be conducted within the United States, regardless of how much test data is available from other sources. 24/ He also feels that FDA reviewers are overly cautious in approving new drugs simply because they are so quickly attacked for having approved a drug which eventually shows toxicity, while they are rarely questioned as to why they did not approve a drug. FDA regulations require drug manufacturers to complete a certain number and certain types of tests. The carrying out of these tests is time-consuming and costly, and, some feel, unnecessary. Futhermore, if long-term toxicity studies are required prior to approval, the target patient population is denied the benefit of the drug for that period of time. Dr. Gilbert McMahon, immediate past president of the American Society for Clinical Pharmacology and Therapeutics and a drug investigator for 31 years, testified at congressional hearings in June 1979 expressing his displeasure with the U.S. drug regulatory system:

> During the past 10-15 years, Federal regulations have become so pervasive, picayune and difficult

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24/ Lasagna, Louis. The Development and Regulation of New Medications. Science, vol. 200, May 26, 1978: 872.

> that today 40% of all new drugs discovered in U.S. companies are first studied outside the U.S. 25/

Although regulatory burdens may in fact be part of the reason why U.S. firms develop drugs in other countries, there are other influencing factors. One study summarized these in the following manner:

> Since research and development is an activity in which highly trained scientific and educated personnel are critical inputs, the availability and costs of such personnel also can be expected to influence these shifts. In addition, differences in the tax treatment of research and development and legal factors such as tort liability and patent protection may greatly influence location decisions. 26/

Donald Kennedy, throughout his tenure as Commissioner of FDA, refuted the charge that the U.S. lagged behind other countries in the introduction of new drugs. He raised three points in particular. First, he made the distinction between the quality of available drugs (in terms of safety and therapeutic efficacy), and the quantity of available drugs. Second, citing a study by Nicholas A. Ashford, et al., he claimed that a multitude of factors, only one of which could be considered "regulatory," affect international drug innovation rates. Other factors include the multi-national character of many pharmaceutical companies and differing

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25/ McMahon, Gilbert. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology; unpublished. June 21, 1979: 2.

26/ Kennedy, Donald. A Calm Look at 'Drug Lag.' Journal of the American Medical Association, vol. 239, January 30, 1978: 426.

rates of exchange. Finally, different countries regulate drugs based on different policies. This country's system is based on documentation, the protection of human test subjects, democratic procedures, and openness and accountability--all of which cost time. 27/

Industry officials and drug investigators have repeatedly said that a decrease in pre-market testing would have little effect on the safety and efficacy to be found in approved drugs. They say that it is in the marketplace where the nature of a drug becomes fully disclosed. FDA Commissioner Kennedy also believed this; but it is for that very reason that FDA is so cautious in approving drugs--because so little is known about them. Commissioner Kennedy drew a rather interesting analogy between FDA responsibilities with drugs and a physician's responsibilities with his patients:

> If a physician were required to practice under similar conditions--access to only a fraction of the patient's history, no ability to modify the diagnosis or the treatment protocol and full accountability for the outcome--there would, I suspect, be a similar tendency toward conservatism. So it is with FDA; given the limitations under which the law requires us to operate, we seek to find out as much as we can before we grant approval. 28/

In a more recent statement, Commissioner Kennedy emphasized that the decline in new drug approvals actually began prior to 1962. After a peak in the

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27/ Kennedy, Donald. Creative Tension: FDA and Medicine. The New England Journal of Medicine, vol. 298, April 13, 1978: 848.

28/ Ibid., p. 849.

mid-50s, a major reduction took place in the years 1959 to 1962 -- before the enactment of the 1962 Amendments. He also said that, in spite of the decline, the number of new drugs showing significant therapeutic gain decreased slightly, if at all. 29/

Others attribute the decline in drug development to the changing scientific climate. Some government and industry officials feel that the current slow rate of drug approval is being unfairly compared with a period that may have been a peak in drug development history, when breakthroughs were numerous and followed one after another. As the field matured, and science advanced from the more obvious to the more obscure, innovation may have slowed its pace. Charles S. Brown, executive vice-president of administration for Abbott Laboratories made the following comment:

> I get the gut feeling that there is an encouraging number of new drugs in the pipeline, but we're getting down to things that deal with human beings at the cellular level...The products themselves are more sophisticated...so we have the same or more information in the pipeline, but fewer products, because each is so sophisticated. 30/

Commissioner Kennedy has repeatedly stated that the decline is scientific, not regulatory, and that it probably involves the relative depletion of

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29/ Testimony of Donald Kennedy, June 21, 1979, pp. 4-5.

30/ Why Drugmakers Fear Reform. Business Week, April 17, 1978: 134P.

one source of knowledge and the vast extension of another. 31/ The diseases of greatest concern that face the public today--such as cancer, cardio-vascular disease, and arthritis--are complex in nature and difficult to treat. A former president of the Merck, Sharp and Dohme drug company characterized the decline as an "apparent exhaustion of certain basic knowledge in which the industry's earlier breakthroughs were based." 32/

Concomitant with the concept that a pool of knowledge is being exhausted is the fact that now more is known about the action of drugs and their potential to cause harm. Thus, increased testing that may be more difficult to conduct appears to be necessary.

The DHEW Review Panel on New Drug Regulation examined the delay in drug development from innovation to market, and their conclusions regarding the causes of the delay summarize those already mentioned and suggest another:

> Enactment of a system of pre-market regulation necessarily affects the cost and time involved in marketing new products. Although the 1962 Amendments thus may provide a partial explanation for recent increases in the cost of drug development and decreases in the number of new drugs approved annually, there has been insufficient testing of alternative hypotheses and causes. For example, the alleged decline in drug innovation also may have been caused by the depletion of technological opportunities for drug development, the advent of more stringent scientific standards for establishing safety and effectiveness, the influence of government

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31/ Kennedy, Donald. A Calm Look at 'Drug Lag.' Journal of the American Medical Association, vol. 239, January 30, 1978: 424.

32/ Ibid.

participation in drug-related research, and a series of mergers within the pharmaceutical industry in the late 1950s and 1960s. 33/

Some foreign countries which have been named in support of the charge that the U.S. is lagging behind in marketing new drugs, have begun to strengthen their own drug regulations. These changes reflect a possible trend in recognizing that more stringent requirements may be desirable to prevent drug tragedies and assure safer products. The changes are occurring in testing and review requirements, efficacy requirements, and in post-approval surveillance programs. In June 1979, FDA Commissioner Kennedy described several recent and on-going efforts in international cooperation in standardizing requirements for new drug approval. Other countries are also referring to U.S. guidelines in developing their own. 34/ It is hoped that such efforts will lead to the reduction of unnecessary and duplicative testing.

FDA has implemented several procedures which reduce or eliminate the lengthy process of filing an NDA. In some cases, "me-too" drugs are not required to undergo the extensive testing that the original drug did. 35/ Depending upon the nature of the drug, FDA may require only limited amounts of information from the manufacturer, in the form of an "abbreviated NDA" (ANDA). This would eliminate the need for full NDA's and, in some

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33/ Review Panel on New Drug Regulation. Department of Health, Education, and Welfare. Final Report, May 1977, p. 30.

34/ Testimony of Donald Kennedy, June 21, 1979, pp. 13, 19-20.

35/ Morey, Richard S. Duplicate Clinical Testing in a Less Than Perfect World. Food Drug Cosmetic Law Journal, vol. 34, February 1979: 123-124.

53-690 O - 79 - 3

instances, eliminate duplicative clinical studies. One of the provisions of the 1962 Act required that drugs approved prior to 1962 be re-evaluated for efficacy. Under the Drug Efficacy Study Implementation (DESI) program, some drugs may be "re-approved" upon submittal of an ANDA. Any changes in the manufacturing or labeling of an approved drug requires FDA approval; such changes, however, can be made by submitting a "supplemental NDA" for approval.

In addition to the drug classification system and the ANDA procedure, Commissioner Kennedy outlined several other steps FDA has taken to reduce unnecessary delays in new drug approval:

-- increased communication between FDA and drug sponsors to clarify what evidence is required to demonstrate safety and efficacy;

-- special handling of promising "breakthrough" drugs;

-- encouragement for drug sponsors to submit certain information early;

-- invitation to PMA to propose standard formats and data presentations for various drug groups;

-- drafting of a Staff Manual Guide to assure effective meetings with industry;

-- increased monitoring of in-house evaluation processes; and

-- development of guidelines for the uniform evaluation of IND's and NDA's. 36/

36/ Testimony of Donald Kennedy, June 21, 1979, pp. 16-18.

Efforts such as these, as well as the legislative proposals in the 96th Congress (see Chapter VIII) are designed to increase expeditious approval of drugs in this country. Whether these efforts will achieve the desired results remains to be seen. Under existing authority and procedures, FDA is capable of speedy approval. In one instance, FDA approved a drug in a matter of days; in 1975, when the Commissioner of FDA, Dr. Alexander Schmidt, was asked if such quick approval will ever happen again, he replied:

> Yes. Interestingly enough, there might be...If there is a new chemical entity that would be terribly important, I would hope that we could react accordingly. 37/

The Government, the drug industry, the medical profession, and the public are all in favor of expediting the new drug approval process. It seems apparent, however, that to accomplish this, the present regulatory system and internal FDA situation will have to be modified.

D. Problems and Limitations Within the FDA

Internal FDA procedures and policies concerning drug regulation have been the target of criticism and appraisal by congressional subcommittees, the drug industry, review panels, and individuals, including agency personnel. Congressional hearings on the quality of drug investigations revealed that limited manpower and resources were major impediments in

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37/ The 1975-1978 Hearings on Drug Testing, Part I, pp. 71-72.

monitoring and regulating such tests. Limitations in FDA's authority are also purported to contribute to the problems.

In 1975, Dr. Schmidt testified that at that time there were approximately 12,000 active drug investigators, 9,000 functioning institutional review committees, 500 pre-clinical laboratories, and 50 commercial testing facilities, and that it was impossible for FDA to undertake direct monitoring of each. He indicated, however, that improvements were possible, mostly in the area of manpower:

> To carry out our monitoring as well as we would like, we would need a fairly large number of highly skilled and well-trained professionals. I would not say that we now have all of the right kind of people that we need. 38/

This is reminiscent of the 1968-1969 hearings on drug testing when Dr. Herbert Ley, then Commissioner of FDA, commented on the ability of the agency to monitor approximately 15,000 investigators:

> I am not satisfied with our total effort in this area today, Senator. This is a problem, of course, with every administrator, trying to balance one need against another. I would like to see more effort in this. On the other hand, I do not believe that anyone could be expected to visit every one of the 15,000. 39/

At a conference on July 11, 1978, Dr. Alexander Schmidt mentioned that one of his most serious problems while FDA Commissioner was the recruitment

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38/ The 1975-1978 Hearings on Drug Testing, Part I, p. 13.

39/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5708.

of staff, adding that this problem could not be solved by legislation. According to the conference report, he seemed to feel that the solution lay with the use of advisory bodies:

> [Schmidt] feels that advisory committees are crucial to the future of the Agency, and that a more formalized structure with regard to their constitution and duties is necessary. In Dr. Schmidt's opinion the credibility of the FDA can only be achieved when the public has confidence that the best possible people are making the decisions. Since it is virtually impossible to have the best qualified people within the FDA, these experts must serve in an advisory capacity. 40/

Thus, the manpower problem at FDA is a recurrent theme. Although improvements have been made over the years, it seems that FDA's ability to attract quality staff remains a significant concern.

Congressional hearings in 1975 (41/) revealed another problem within FDA which contributed to poor communication and ineffective procedures. It seems that in some cases involving questionable test data and submittals, important documents and memoranda were lost within the agency, or never reached their intended destinations, and some actions initiated were never followed up.42/ Whether or not these situations still exist within the agency is unknown; it does not appear to be an area of concern in current drug literature.

40/ Center for the Study of Drug Development. Report of Washington Conference on The Drug Regulation Reform Act of 1978 (conference held in Washington, D.C. on July 11, 1978). November 1978. p. 1.

41/ The 1975-1978 Hearings on Drug Testing, Part I.

42/ Ibid.

In 1977, Dr. J.E.S. Parker, Senior Lecturer at Otago University in New Zealand, published an economist's view of the United States' drug regulatory process and its effect on pharmaceutical innovation. 43/ In his analysis, Dr. Parker made a number of observations on deficiencies and problems within FDA. Among his observations were the following points:

-- FDA must work in a political climate as well as medical; and political criticism of scientific judgment may be ill-informed;

-- FDA was mandated to guarantee the efficacy and safety of new drugs, and while such standards are easy to legislate, they are extremely difficult to implement;

-- FDA is a large, slow-moving, relatively inflexible department of government, lacking a degree of independence; a faster-moving, more flexible organization with some degree of independence would be more desirable;

-- the incentive at FDA is negative--there is no positive reinforcement for prompt decisions and efficient approval of beneficial new drugs; rather the motivation lies in the consequences of passing a "bad" drug--thus there is a predisposition toward caution;

-- jobs which require professionals to appraise the research work of others are less likely to attract top quality men who would generally prefer to pursue independent research--yet such a job requires expertise;

-- in the U.S., the interchanges between FDA and the drug firms are almost entirely in document form, with little informal contact--this reflects an atmosphere of distrust, and eliminates the most effective form of communication;

43/ Parker, J.E.S. Regulating Pharmaceutical Innovation: An Economist's View. Food Drug Cosmetic Law Journal, vol. 32, April 1977: 160-181.

-- the emphasis on pre-market testing, the rare use of monitored release and the weakness of post-marketing surveillance procedures, indicates too high a degree of faith in simulation; and

-- FDA tends to operate on the attitude of "absolute risk," where "bad" drugs must be weeded out to protect the public from harm; "relative risk" would concentrate more on medical progress and relief of illness and less on consumer protection, but such an attitude would require a sophisticated and sensitive post-approval system.

In his report, Dr. Parker implies that these points contribute to delays in approval and adversely affect drug innovation. He concentrates on the fine operational mechanisms and attitudes necessary for an efficient system.

The DHEW Review Panel on New Drug Regulation, on the other hand, examined FDA from the viewpoint of authority limitations as well as operational deficiencies. The Panel was chartered in February 1975 and one of the several tasks assigned it was to study current policies and procedures of FDA relating to the approval and disapproval of new drugs. Although the Review Panel concluded that the present system of evaluating new drugs on the basis of safety and efficacy was sound, it found that the implementation of the regulatory system needed substantial improvement. These improvements were seen as falling into four areas: making the review process more open and accountable to the public, increasing FDA's scientific capabilities, improving standards and procedures for pre-market approval of new drugs, and increasing FDA's authority in the post-marketing period. 44/

44/ Final Report of the Review Panel on New Drug Regulation, May 1977, p. 2.

In one of their interim reports, the Panel suggested that FDA should be able to limit the distribution of drugs demonstrating unusual benefit but also showing unusual toxicity. They further examined the several disadvantages to such authority. 45/ The Panel also believed the FDA should be given the authority to release a drug prior to the completion of Phase 3 studies when the benefits of the new drug warrant such action.

The role of FDA in the post-approval period is extremely limited. The agency can only threaten withdrawal of a drug, and does not have the authority to place conditions on the approved product. The Review Panel stated that this role should be expanded; FDA should be able to require further studies, such as when a drug is used for an unapproved use. More importantly, once a drug is approved, it is relatively free of controls; the Panel found that FDA should have the authority to develop a system for monitoring approved drugs. With this authority, it is believed that the approval process for new drugs could be shortened:

> The fact that FDA plays such a minimal role in post-marketing regulation of new drugs is inconsistent with its responsibility to protect the public from unsafe or ineffective drugs. In addition, because it has little control over approved drugs, the agency may be overly cautious in granting approval. 46/

45/ Review Panel on New Drug Regulation. Department of Health, Education, and Welfare. Interim Report: Expansion of FDA's Statutory Authority in the Post-Marketing Period for New Drugs. April 25, 1977, p.9.

46/ Final Report of the Review Panel on New Drug Regulation, May 1977, p.92.

One effort aimed at expanding FDA's post-marketing role was the formation of the Joint Commission on Prescription Drug Use. The Commission was a result of a request from Senator Edward Kennedy to the pharmaceutical industry. Sponsored by the Pharmaceutical Manufacturers Association (PMA), the Commission is made up of representatives from major elements of the health community. Its duty is to study methods to develop a system for collecting data on drug use and adverse effects, and for evaluating the effects of such use. A second effort in this area is the cooperation between FDA and the National Bureau of Standards to explore the possibility of establishing a comprehensive system for post-approval surveillance of new drugs, primarily to identify adverse reactions.

It should be noted that many of the issues presented by critics of FDA are addressed by legislation currently pending in the 96th Congress. This legislation is discussed in Chapter VIII.

III. SELECTION OF DRUG INVESTIGATORS AND PAYMENT

A. 1968-1969 Hearings

It is the responsibility of the sponsoring drug firm to select investigaotrs to carry out the testing required on any new drug product. It was recognized in the 1968-1969 hearings before Senator Nelson's Subcommittee on Monopoly that the objective of the drug firms is to produce safe and effective drugs. While the profit motive cannot be overlooked, it is to the company's advantage to produce quality products. Thus, the firms subject each new drug to a battery of tests. These tests may be conducted in the firms' own laboratories or contracted to outside investigators. It is after the basic "laboratory" testing, involving animals, that a drug is tested in "clinical" studies involving human subjects. The selection of qualified investigators for these clinical trials is extremely important. Dr. Herbert Ley, Jr., then Commissioner of Food and Drugs, said in testimony that:

> Ideally, phase 1 studies [when the drug is first tested clinically] should be undertaken primarily by an individual qualified to observe subtle pharmacological effects during initial trials. He should have adequate facilities for investigation with respect to patients, clinical laboratory services, and time to devote adequate attention to such studies. 47/

In their report on the controversial Alabama prison studies, discussed later, the Alabama Medical Association stated that "It is our opinion

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47/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5643.

that Phase 1 studies, in general, and, in particular, those involving a first human testing, do not give sufficient importance to either the choice of the investigator or the briefing of the investigator." 48/

Two points were addressed during the Nelson hearings with regard to investigator selection: 1) the qualifications and abilities of the drug tester, and 2) the resulting relationship between the sponsoring firm and the investigator. In regard to the qualifications of investigators, Dr. A. Dale Console, a former director at E.R. Squibb & Sons, in a written statement to the subcommitee, described much of drug testing as being "humdrum" and uninteresting, while only a small percentage of new drugs were truly exciting and thus attractive to well-qualified and highly respected researchers. He stated that the less glamorous drugs must also be studied "...and in trying to find 'investigators' who are willing to do the job, one must scrape the bottom of the barrel." 49/ The belief that there existed a lack of trained available investigators was echoed by several witnesses during the hearings. The second point brings up the question of possible "bias" on the part of the researcher who is evaluating a product for a drug

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48/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5694.

49/ U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Competitive Problems in the Drug Industry. Hearings, 91st Congress, 1st Session; Vol. 11. Hearings held February 19, 20, 26, 27, March 13, 18, 25, and 26, 1969. Washington, U.S. Govt. Print. Off., 1969. p. 4481.

sponsor who undoubtedly would like to see favorable results. This concern was examined from two viewpoints: 1) the nature of the investigative situation--that is, whether the "investigator" is an institution, such as a medical school, teaching hospital, or research facility, or if it is an individual physician or researcher; and 2) how the investigator is paid.

Drug firms usually contract their testing to either a solitary investigator or to an institution, such as a medical school or teaching hospital. It was felt that objectivity is easier to maintain in the medical school setting than with an individual investigator who relies on the drug firm for financial support and the possibility of future contracts. During testimony, Dr. Franz J. Inglefinger, editor of the New England Journal of Medicine, made the following statement regarding this issue:

> It is my impression that the objectivity of such studies and the freedom from undue influence related to the source of support depends a great deal on the circumstances under which this testing is carried out. Currently, at least, the testing is often carried out, (a) in a medical school setting, and this means that administrative officials rather than the investigator will handle the financial arrangements; that is, with no direct payment to the investigator, and (b) which, I think is also important, others besides a solitary investigator, that is, technicians, referred to by Dr. Lowinger, graduate students, other physicians, house officers, will participate in the test procedures. These young people are some of the most severe critics in the world, and their involvement in this type of work makes it very difficult, I think, to judge the results. So I think the study of this type is safeguarded, in that there is participation by a number of people who have no financial interest in the nature of the results. 50/

50/ The 1968-1969 Hearings on Drug Testing, vol. 10, p. 4019.

In addition to the financial ties which might affect objectivity, Dr. Inglefinger stressed the generally superior facilities of research institutions. In speaking of the delicate analysis required in the more advanced phases of drug evaluation in humans (for example, to assess risk and benefit), he said:

> The desires of both patient and investigator may color the interpretation. Hence, studies of this type must be carried out under optimum conditions ...optimum conditions mean investigators who are equipped by training and facilities to carry out such testing, and who use a protocol incorporating procedures that characterize a well-controlled study. If these conditions are observed, I doubt that the results are likely to be influenced in any way by subtle economic pressures. However, if a study is carried out by an individual without such facilities, without a protocol which is generally accepted as being satisfactory, and under direct payment of that individual evaluating that study, possibly in a solo private office setting where the facilities are not available, I would disapprove of such studies. 51/

It was apparant in the hearings that Dr. Inglefinger did not intend to categorize all institutionalized research as good, and all individual testing as suspect; he merely attempted to describe certain safeguards and pitfalls inherent in each. The general impression from the hearings, however, was that more valid test data could be expected from an institution where the facilities are generally better, protocols may be more closely followed, standards are maintained, and adequate training of staff is better assured.

51/ The 1968-1969 Hearings on Drug Testing, vol. 10, p. 4020.

Dr. William O'Brien, in an article appearing in the Bulletin of Atomic Scientists (Jan. 1969) and re-printed in the hearings, noted that investigators in medical universities do occasionally receive personal honoraria from drug firms, outside the framework of salary scales. The research programs of many of the investigators are largely supported by the National Institutes of Health (NIH), but according to Dr. O'Brien, "Some of these investigators seem far more concerned about the welfare of the pharmaceutical industry than they do about the tax-paying public, even though the public actually provides most of their support." 52/ That the investigator should feel more patronage from, and duty to, the pharmaceutical houses than to the public lends credence to the suspicion that bias can occur, knowingly or unknowingly. Dr. Console also pointed out that an appeal to the ego was often as enticing as money.

The subcommittee expressed concern over the fact that testing carried out in a public institution was not fully supported by the firm sponsoring the drug studies. Dr. Paul Lowinger, a teacher and drug investigator at Wayne State University, testified that his contracts were generally made between the drug firm and the university with which he was affiliated, but that the firm only paid for limited items such as laboratory tests, secretarial time, some time by resident physicians, and some of the technicians' time; the firm did not pay the school to cover the principal investigator's salary for his time or skill, nor did they pay for overhead, such as materials and equipment, use of the facilities, and so forth. 53/

52/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5753.

53/ Ibid., vol. 10, pp. 4004-4006.

Senator Nelson compared this system with that of research sponsored by NIH at Wayne State University, saying that NIH pays the full salaries of everyone involved and computes an overhead cost of the physical facilities. He equated the drug firm/research institution relationship with "subsidized research," asking:

> Why should any publicly supported institution in the country--why should the taxpayers in any State be paying the cost of investigations which are being done in behalf of a profit-oriented corporation? Why shouldn't the corporation pay all of it? 54/

The implications of a drug firm directly paying a solitary investigator have already been indicated. Feelings of loyalty, obligation, or the prospect of continued contracts might affect the researcher's objectivity. Dr. Console expressed his opinion on the situation as follows:

> Both because there are doctors who are incorruptible and because someone must pay for drug testing, I think it is wrong to damn monetary rewards in a blanket fashion. I do believe, however, that clinical testing and the choice of investigators should be taken out of the hands of the drug industry. So long as we have a system that allows drug companies to buy the claims that will sell a drug, we have a potentially corrupt system. I am convinced that the public interest will best be served when we devise a system that preserves anonymity between the drug company that has a proprietary interest in a drug and the investigator whose research results may or may not supply the claims that will sell the drug. 55/

54/ The 1968-1969 Hearings on Drug Testing, vol. 10, p. 4006.

55/ U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Competitive Problems in the Drug Industry. Hearings, 91st Congress, 1st Session; Vol. 11. Hearings held February 19, 20, 26, 27, March 13, 18, 25, and 26, 1969. Washington, U.S. Govt. Print. Off., 1969. p. 4481.

The Food and Drug Administration (FDA) maintains a list of clinical investigators designated by drug sponsors, and while the agency does not "approve" investigators, it can declare an investigator ineligible to receive investigational drugs. Such disqualification would be based on a field audit of the clinical trial. In 1969, FDA had approximately 15,000 investigators listed, and according to the testimony of Dr. Herbert Ley, then Commissioner of FDA, it was simply not possible to audit every single one. Clinical trials, then, were usually selected for audit only if something looked suspicious to the FDA reviewers, such as:

1) questionable qualifications of the investigator;

2) suspicion of irregularities based on IND or NDA data;

3) unusually large quantities of testing undertaken by a single investigator in a given period of time;

4) reports indicating higher than normal frequency of disease in a test population;

5) complaints from sponsoring firms; or

6) exaggerated or misrepresented claims in summaries published prior to FDA approval. 56/

At the time of the hearings, FDA had disqualified eleven investigators, three of which were reinstated after conforming to FDA standards. The faults found with these investigators and their drug trials included: false reporting, low standards, faulty procedures, substitution of cases, poor facilities, untrained personnel, "doctored" records, too many

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56/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5645.

studies undertaken at one time by a single investigator, lack of supervision by the researcher, complete absence of the researcher, and inadequate and false records. 57/

Members of the drug industry itself also recognized that problems existed in the quality of clinical work, largely due to the quality of investigators. Speaking about the low quality of published clinical work, a 1969 news article in the Washington Post reported:

> This fact often is held against the drug industry, Drs. H. Bloch of CIBA, Ltd., in Basel and G.E. Paget of Smith Kline & French Laboratories, Ltd., acknowledged...But, the two doctors said, "it is as much to industry's disadvantage as to medicine's that this situation exists. This unsatisfactory state of affairs does not come about because industry seeks third-rate investigators to carry out these [drug testing] trials in the hope that they will thereby obtain an unreasonably favorable outcome...It arises because of the dearth of investigative facilities and first-class investigators throughout the world." As they saw it, the answer lies in "a complete revolution in the attitude of medical schools and teaching hospitals to the clinical investigation of drugs and the training of investigators." 58/

B. 1969-1979

While the selection of drug investigators has not been a major issue in the literature since the 1968-1969 hearings, the necessity of selecting qualified individuals to conduct drug testing is still a critical factor in drug development. A Department of Health, Education,

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57/ The 1968-1969 Hearings on Drug Testing, vol. 14, pp. 5645-5649.

58/ Ibid., p. 5747.

53-690 O - 79 - 4

and Welfare (DHEW) publication on investigational drug procedures broadly describes the qualifications necessary for investigators in clinical testing:

> The training and experience needed will vary, depending on the kind of drug and the nature of the investigation. In phase 1, the investigator must be able to evaluate human toxicology and pharmacology. In phase 2, the clinicans should be familiar with the conditions to be treated, and the drugs used in these conditions and the methods of their evaluation. In phase 3, in addition to experienced clinical investigators, physicians not regarded as specialists in any particular field of medicine may serve as investigators. 59/

In 1975, Dr. Alexander Schmidt, then Commissioner of FDA, testified before two Senate subcommittees (Committee on Labor and Public Welfare, Subcommittee on Health, and Committee on the Judiciary, Subcommittee on Administrative Practice and Procedure). While commenting on the quality of drug research and the surveillance of these tests, he made the following statement:

> One of the greatest problems is the current reward system in science, which has generally deemed much of drug research unworthy of recognition...A second major problem is that the sheer numbers of investigations required by the 1962 Amendments guarantees that not all investigators will be highly qualified and deeply interested in the drug they are studying. Many studies are, and will continue to be, conducted by relatively inexperienced physicians who must be monitored closely. 60/

59/ U.S. Department of Health, Education, and Welfare. Food and Drug Administration. Clinical Testing for Safe and Effective Drugs. [DHEW Publication No. (FDA) 75-3015] p. 3.

60/ The 1975-1978 Hearings on Drug Testing, Part I, p. 12.

The fact had been brought out in the 1968-1969 hearings that it was the responsibility of the drug sponsor to oversee its investigators and to assure that they conformed to regulation. The FDA did not, and does not, approve investigators; FDA can, however, disqualify investigators who do not meet FDA standards. By 1970, FDA had declared a total of seventeen investigators ineligible to receive investigational drugs. These individuals had been investigated "for cause"; that is, FDA had cause to suspect poor performance based on the six points mentioned in the preceding section. In 1972, FDA broadened its review of investigators to increase coverage beyond that of inspections only "for cause." A two-year survey was initiated (July 1972-June 1974), in which sponsors and their investigators were inspected. At the completion of this survey, 155 investigators had been inspected. FDA concluded that only 26% were found to be performing satisfactorily in every compliance area. Of the remaining 74%, most were found not to have committed serious violations. The investigators were rated in these six compliance areas:

1) patient consent
2) drug accountability
3) protocol adherence
4) study role
5) records availability
6) records accuracy

In view of the survey results, Dr. Schmidt remarked:

> I believe the survey results can thus both reassure us that grossly violative practices are infrequent, and disturb us because the more minor deficiencies are so frequent. There is obviously a common inattention to details that are important to high

> quality research. There is obviously also a small fraction of investigators who have not been adequately warned of serious deficiencies, who deserve very close and frequent scrutiny, and who should be disqualified if deficiencies are not promptly corrected. 61/

The question of bias continues to be a concern in the area of drug investigation and payment. Bias can occur at the drug firm level or at the investigator level, or both. Its manifestation at the industry level may be conscious or unconscious, and may take the form of fraudulent or misleading data submitted to FDA. Because of financial ties, enthusiasm and bias on the part of the drug sponsor may influence the investigator. In their May 1977 final report, a DHEW Review Panel on New Drug Regulation reached the following conclusion:

> While personal bias in the collection and analysis of scientific data probably can never be eliminated entirely, it can be reduced considerably. The most direct means of minimizing the bias in testing is to have research conducted by investigators who are financially independent of the drug sponsor. 62/

61/ The 1975-1978 Hearings on Drug Testing, Part I, p. 92.

62/ Final Report of the Review Panel on New Drug Regulation, May 1977, pp. 85-86.

IV. QUALITY OF DRUG TESTS

A. 1968-1969 Hearings

On several occasions, witnesses at the 1968-1969 hearings made it clear that, by and large, a majority of the tests carried out under the sponsorship of drug firms were conducted capably and with a high degree of professionalism and quality. Substandard testing did occur on occasion, however. The exact extent to which this occurred was not known since it was not feasible for FDA to audit every drug trial. Since the quality of a test is often apparent from the resultant data, and since FDA depends heavily on submitted data, it should be noted the the agency does not require that all raw data on animal studies be submitted, whereas it does require this information from clinical research studies.

Dr. Herbert Ley described some of the substandard test conditions which had been brought to the attention of FDA. These included: inadequate record-keeping; modified or changed entries differing from original results; false reporting of test results to the sponsor or FDA; the use of the same human or animal subjects in concurrent trials; lack of supervision by the investigator over the trials; inadequate test populations in regard to size; and so on.

One example of substandard testing was discussed at length in the 1969 hearings during the testimony of FDA Commissioner Ley. Dr. Austin R. Stough was a general practitioner who had conducted drug studies in the Alabama prison system. Dr. Stough's studies were questionned for several reasons: poor record-keeping; inaccurate records; inadequate physical examinations; and inadequate medical supervision of the volunteer

test subjects. Dr. Stough was first brought to the attention of FDA because of a hepatitis epidemic among prisoners; this was subsequently proven to have been the result of Dr. Stough's poor technique in the conduct of a plasmapheresis* program. 63/ Dr. Stough's involvement with plasmapheresis was discontinued and subsequent attention centered on his drug studies. Early FDA evaluations of Dr. Stough's studies revealed no inadequacies under FDA regulations, although certain deficiencies were apparent in the trial methods. The Acting Director of FDA's Bureau of Medicine, Dr. John Jennings, concluded a memo to Dr. Ley by stating:

> Although...two investigations of Dr. Stough's operations disclosed no violations of our regulations, obviously we should be concerned that such an operation can exist under current regulations of FDA and DBS [Division of Biologic Standards]. Aside from the welfare of the subjects, the question of validity of the studies may still be raised--especially the possibility of concurrent testing of drugs. 64/

Dr. Ley's testimony stressed the lack of monitoring over Dr. Stough's studies. Had there been a review committee monitoring the studies, the problems which did arise would have been unlikely to occur. 65/ After the controversies had been raised and made public, the Alabama Medical Association appointed a special committee to examine the case. The Committee

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* "Plasmapheresis" is a process whereby red blood cells are separated from the blood plasma and returned to the donor, the plasma being collected and used for other purposes.

63/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5681.

64/ Ibid.

65/ Ibid., p. 5685.

indicated in their report that it was the responsibility of the Alabama Board of Corrections to maintain internal control over the testing program. They felt that it should be the duty of the medical member of the Board to briefly review the protocols for each new drug trial. 66/ Dr. Ley, on the other hand, felt that the Alabama Medical Association also had an oversight function in terms of the physicians operating within the State. Although the Association eventually did what amounted to "peer review," Dr. Ley felt perhaps this responsibility could have been fulfilled earlier. 67/

During its investigation of Dr. Stough's drug trials, the Alabama Committee found several deficiencies, including: inadequate explanations given to the prisoners regarding the tests; lack of medical supervision; insufficient physical examinations; severe reactions to the drugs tested; lack of medical care for the subjects; appalling conditions in the medical facilities; and untrained personnel and prisoners carrying out medical responsibilities. It was noted that these deficiencies were not found at all of the prisons involved in the drug trials; where the testing appeared to be of better quality, the Committee gave due credit to concerned prison officials. Regarding the data generated from Stough's studies, the Alabama Committee noted:

> ...the research studies completed and published in highly respected journals...represent creditable, useful, and practical contributions to medical science. However, this good should not be permitted to hide the manifest defects in the present system. 68/

66/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5690.

67/ Ibid., p. 5605.

68/ Ibid., p. 5692.

It was also the opinion of the Committee that the facilities at one prison did not meet even minimal standards. Furthermore, it was felt that Dr. Stough's company laboratory, while well-stocked and equipped, was operated under negligent and substandard techniques. It was the Committee's opinion that results from this lab were "generally but not always accurate." 69/

Although the Alabama Committee found no deliberate wrong-doing on the part of the sponsoring drug firms, who had contracted with an "approved" (i.e. not disqualified) investigator to conduct approved research, it did suggest 1) that the firms' monitoring of the trials had been too superficial; 2) that the phase 1 investigator should have been selected with more discretion; and 3) that perhaps the investigator should have received a better, more comprehensive briefing on the drug he was about to test in humans. 70/ The Committee went on to say:

> There is no reason to doubt that excellent programs are desired by the drug manufacturers or that they would support such programs. Despite this, both the drug firms and FDA have given tacit approval based on their confidence in the reliability of data so obtained. 71/

It should be noted that in this case, and others like it, while substantial defects were found in the testing program, the trials could serve a useful purpose, and in Dr. Stough's case, did contribute to the increased knowledge of drugs. The quality of drug tests most seriously affects the human subjects (this topic is discussed more extensively in

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69/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5693.

70/ Ibid., p. 5694.

71/ Ibid., p. 5695.

another chapter of this report). In summarizing the Stough incident, the Alabama Committee said:

> It is the unanimous opinion of this committee that the drug testing program is almost essential and should be continued for the benefit of the prisoners and society in general. However, as presently conducted the program does not provide adequate safeguards for the health of the prisoners and leaves something to be desired in quality of results obtained. 72/

The Stough incident brought up a question which was never fully answered in the hearings: Who is responsible for monitoring such trials -- the drug firm, the institution housing the subjects (such as prisoners), State authorities, an independent review committee, or the FDA? Under questioning by Senator Nelson, Dr. Ley described the limited manpower, resources, and authority in FDA to monitor investigational trials. Under regulatory authority, he said, it was the drug sponsors' responsibility to supervise the trials and insure their quality. 73/

B. 1969-1979

Like the issue of selecting investigators for drug testing, the subject of test quality has become somewhat overshadowed by new drug issues. Nevertheless, throughout the 1970s, the quality of the tests has continued to be recognized as the basis upon which new drugs are evaluated and their usefulness determined.

72/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5701.

73/ Ibid., p. 5678.

Perhaps the major concern today in drug development and regulation is the delayed approval for new drugs. Drug researchers and firms complain that once a New Drug Application (NDA) is submitted, FDA usually takes an unreasonably long time to act on the application.

Wayne L. Pines, editor of the FDA Consumer in 1974, attributed most of the delay to inadequate data submittals to FDA. He stated that:

> Studies were not well controlled or there were not enough. In a large number of cases there was inadeuqate information about the manufacturing and quality control. 74/

In approving or disapproving NDAs, FDA must rely on data submitted by the sponsors. Careful scrutiny of the data by FDA reviewers is required to ascertain whether or not the testing has been conducted adequately and completely. Poorly conducted studies may lead to doubt about the integrity of the data generated.

Although critics of the drug development system agree that drug tests are generally conducted adequately and conform to high scientific standards, cases of substandard performance and outright negligence do occur. In 1975 and 1976, two Senate subcommittes (75/) held comprehensive hearings on preclinical and clinical testing by the pharmaceutical industry. Speaking on the quality of drug tests and the data obtained from them, Dr. Alexander Schmidt, then Commissioner of FDA, said:

74/ Pines, Wayne L. A Primer on New Drug Development. FDA Consumer, vol. 8, February 1974: 14.

75/ (Senate Committee on Labor and Public Welfare, Subcommittee on Health; and Committee on the Judiciary, Subcommittee on Administrative Practice and Procedure.)

> ...it is a sad truth that for a variety of reasons, much of the clinical work on drugs done in this country is seriously flawed, either because of inattention to proper planning and conduct of the study, lack of skill on the part of the investigator, lack of resources devoted to the subject, or lack of people to do the work properly. 76/

Considerable testimony was heard on deficiencies found in animal tests conducted at and sponsored by G.D. Searle and Co. One of FDA's principal investigators, Dr. Adrian Gross, inspected the Searle operation on numerous occasions. In a summary of his observations, he included the following statement, detailing the deficiencies he found in one particular animal test:

> The Searle rat study reported on in the NDA was of a quality, at best, questionable due to a number of aspects such as limited background and experience of supervisory professional personnel; lack of professional supervision of any kind of technicians making pathology observations; autopsies on experimental animals being carried out in a significantly incomplete manner; the recording of histopathologic observations in such a manner that their reliability could not be verified by anyone, and a number of other observations about the personnel. 77/

Officials from Searle forcefully argued their side of the case, claiming that charges brought by Dr. Gross were unjustified. They explained several of their technical procedures which were being questioned, and attempted to counter FDA's objections to the study. In spite of Searle's rebuttal, FDA's task force, created to examine the animal studies at

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76/ The 1975-1978 Hearings on Drug Testing, Part I, p. 12.

77/ Ibid., p. 58.

Searle, reported unfavorably. Concerning the quality control problems at Searle, the task force said in their final report:

> ...we have found instances of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly executed, or inaccurately analyzed or reported. While a single discrepancy, error, or inconsistency in any given study may not be significant in and of itself, the cumulative findings of problems within and across the studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies. 78/

Searle protested the conclusions of the Task Force asserting that the report repeatedly drew from "isolated, usually insignificant errors, wide ranging statements, engaging in speculation without any perspective whatsoever of the scope or scientific significance of the particular error." 79/ Commenting on the Task Force's information, the Searle Co. later said "this 'supporting' data is so replete with errors, misstatements, mischaracterizations, and unsupported conclusionary statements that reliance upon it for any purpose is unwarranted." 80/

Regardless of who was right or wrong in this debate, this particular case, because it was examined so thoroughly, is significant for several reasons. First, it demonstrates the investigative attitude of the FDA and the contentions of the drug firm in supporting its test procedures. Second, it points outs the different perspectives and opposing

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78/ U.S. Congress. Senate. Committee on Labor and Public Welfare, Subcommittee on Health; and Committee on the Judicary, Subcommittee on Administrative Practice and Procedure. Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part III. Joint Hearings, 94th Congress, 1st Session, on the Examination of the Process of Drug Testing and FDA's Role in the Regulation and Conditions Under Which Such Testing is Carried Out. Hearings held April 8, 9; and July 19, 1976. Washington, U.S. Govt. Print. Off., 1976, p. 4. [Hereinafter included in reference to The 1975-1978 Hearings on Drug Testing.]

79/ Ibid., p. 76.

80/ Ibid., p. 104.

interpretations by two parties looking at the same information, each drawing different conclusions and attaching different degrees of significance to the facts. Finally, this case conclusively proved that the quality of the drug tests and the data generated are not always 100% correct. Whether errors are inevitable in testings and whether such errors are enough to invalidate the test results are difficult questions. In the interest of protecting the public from unsafe and ineffective drugs, FDA apparently acts on the premise that errors are not necessary and they may indeed cast doubt on the integrity of the test data.

In May 1977, the DHEW Review Panel on New Drug Regulation published a final report on the policies and procedures of FDA relating to the approval of new drugs. 81/ While this Panel was subject to criticism itself, many of its observations and recommendations are evident in recent legislative proposals. The Panel made two suggestions which were designed to improve the quality of drug studies -- 1) the development, distribution, and regular revision of guidelines for conducting animal and human studies, and 2) public disclosure of test data. It was felt that if drug companies were well informed about FDA expectations regarding new drug investigation, they would conduct their tests along those lines:

> Formal release of up-to-date preclinical and clinical guidelines should improve the quality of research and increase the acceptability and reliability of test data by clarifying

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81/ Final Report of the Review Panel on New Drug Regulation, May 1977.

> what FDA believes constitutes a well-controlled study and by providing investigators with generalized standards and procedures for conducting animal and human testing. 82/

The Panel's second suggestion was based on the belief that if safety and effectiveness data, which are presently considered confidential, were made available for public review, the drug manufacturers would have a greater incentive to ensure the high quality of those data. 83/ Guidelines have been formulated by FDA, and a list of these guidelines can be found in the Appendices to this report. Legislation presently being considered in the 96th Congress (bill S. 1075) does call for the issuance of guidelines regarding protocols and methods for conducting drug investigations. This bill, however, as it was introduced, would not require public disclosure of full reports of investigations showing safety and efficacy; it would, however, allow for public examination of summaries of data, scientific methodology, and other information obtained from all investigations. Submission of these summaries would constitute a new drug regulatory requirement.

82/ Final Report of the Review Panel on New Drug Regulation, May 1977, p. 67.

83/ Ibid., p. 85.

V. VALIDITY OF TRANSMITTED TEST DATA

A. 1968-1969 Hearings

The quality of drug tests is necessarily related to the selection and capabilities of the investigators. In turn, the resultant test data are greatly influenced by the techniques and standards employed in the trials. FDA depends on the data it receives from drug firms in making its decisions on drug approval, and the drug firms depend on the data they receive from the investigators. Between the time tests are first initiated and when FDA receives the application materials from the drug sponsor, the generated data are transcribed, manipulated, and transmitted several times. Ample opportunity exists for the alteration of the data. Therefore, the information FDA eventually receives could be distorted or incomplete in relation to the original data.

Witnesses before the subcommittee in 1968 and 1969 described various problems with test data ranging from false or misleading data to the omission of data. Discrepancies were reported to have occurred at various stages of drug development -- in the recording of data during trials; in the writing of reports, requiring transfer from raw data; in the transmission of data from investigator to sponsor; and in reports sent by drug firms to FDA for approval. FDA's major complaint was the quality of submittals in INDs and NDAs. Dr. James L. Goddard, a previous Commissioner of Food and Drugs, was reported to have made the following statement in a 1967 speech to members of the pharmaceutical industry:

> I can say that I have been shocked at the quality of many submissions to our IND staff. The hand of the amateur is evident too often

> for my comfort. So-called research and so-called studies are submitted by the carton-full and our medical officers are supposed to take all this very seriously...In addition to the problem of quality, there is the problem of dishonesty in the Investigational New Drug stage...Let us move on to New Drug Applications...I have been shocked at the materials that come in to us. I have been shocked by the clear attempts to slip something by us. 84/

Dr. Ley, Commissioner of Food and Drugs at the time of the 1969 hearings, told the subcommittee that while there had recently been improvements in the submittals of test data to FDA, he still felt that the major problem in drug development was the poor quality of data coming into the FDA files. 85/ Dr. Ley reported that in August of 1966, a program was initiated at FDA whereby all newly received INDs were subjected to an initial screening, and those found inadequate or incomplete were promptly rejected. 86/

Cases were discussed in the hearings which showed that on occasion, investigators and/or sponsors did not report adverse effects. By comparing the work of one investigator with results of others' tests on the same product, FDA was able to spot discrepancies and initiate an audit of the suspect study. For example, the thalidomide and MER 29 episodes occurred prior to the passage of the Kefauver-Harris Amendments in 1962. Both products were reported to FDA by drug firms without disclosure of serious side effects. Dr. Ley felt that the 1962 Amendments did much to rectify

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84/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5668.

85/ Ibid., p. 5674.

86/ Ibid., p. 5644.

a deficient drug approval system by giving FDA the resources to conduct necessary monitoring and oversight functions. Legal reprisal for failure to disclose pertinent information was assumed to be a significant motivator for increased responsibility on the part of drug firms. Although legal action was a possibility before 1962, the Amendments make periodic reporting by the drug firms to FDA mandatory. Efficacy studies were not required prior to the implementation of the Amendments; therefore, applications for new or investigational drugs before 1962 did not have to include these studies, and such information was not considered "undisclosed" if not submitted.

Dr. Lowinger's testimony before the subcommittee in December 1968 emphasized the omission of data from submittals by drug sponsors to FDA. As a drug investigator, Dr. Lowinger was involved in the preparation of 27 reports on drug studies, all of which indicated toxicity. He claimed that the data from only nine of these studies was actually sent to FDA by the drug firms involved. Regarding several of the studies which were not submitted to FDA, the agency told Dr. Lowinger that the reports were not required; in other cases, FDA reported that the studies on a particular drug had been discontinued, or that no IND or NDA had ever been filed. 87/ FDA's response to Dr. Lowinger's query asking if the reports had been received was that prior to the passage of the Kefauver-Harris Amendments in 1962, there was no requirement that FDA be notified of all investigators and investigations. 88/

87/ The 1968-1969 Hearings on Drug Testing, vol. 10, p. 4009.

88/ Ibid.

53-690 O - 79 - 5

One particular product, Dornwal, was found to have toxic effects on the blood. Dr. Lowinger's study of this drug indicated toxicity, but his report was not submitted to FDA. In its letter to Dr. Lowinger, dated March 29, 1968, FDA said "The 1961 report was not located. Not required." 89/ Yet in 1961, the FDA requested of the U.S. Department of Justice that criminal proceedings be instituted against the company producing Dornwal for "knowingly and willingly concealing material information, and submitting and causing the submission of false and fictitious statements." 90/ These charges were not in reference to Dr. Lowinger's report, but rather to other evidence showing the firm's failure to disclose pertinent information. The firm was subsequently convicted on those charges. 91/

Information on the MER 29 case was submitted as appendix material to the 1968 hearings. MER 29, a product to lower cholesterol, was approved by FDA based on data submitted by the sponsoring firm. Later, discrepancies in the test data and methods were uncovered. Persons associated with the animal studies revealed that data had been manipulated -- raw data differed from the data submitted to FDA; some data were omitted; other data were falsified; negligent methodology in the testing was found; determinations were made from animals that had not survived; reports of adverse effects were concealed; and so on. 92/ After extensive investigations by FDA and considerable communication between FDA and the drug's sponsor, the William S. Merrell Co., MER 29 was withdrawn from the market and its NDA suspended.

89/ The 1968-1969 Hearings on Drug Testing, vol. 10, p. 4009.

90/ Ibid., p. 4010.

91/ Ibid., p. 3998.

92/ Ibid., pp. 4202-4209.

B. 1969-1979

The validity of test data has remained a critical issue in sound evaluation and approval of new drugs. If approval of an IND or NDA is granted based on false, fraudulent, misleading, or incomplete data, then the approval is without value, and physicians and consumers are mistakenly assuming that such a product is safe and effective. The distinction should be clearly made that while varying or even opposing interpretations can be drawn from a given set of facts, the basic integrity of data submitted is not subject to debate. Altered data, false or misleading statements, and deliberate or accidental omissions of relevant information prevent adequate evaluation of drug products.

Between 1975 and 1978, extensive congressional hearings were held to discuss problems in preclinical and clinical testing by pharmaceutical companies. 93/ At that time, FDA had uncovered deficiencies in the animal tests conducted by several drug firms and private research laboratories. The most comrehensive discussions concerned the situation at G.D. Searle & Co. This case has been discussed in the chapter on test quality, but is equally pertinent to a discussion of valid test data submittals.

Dr. Adrian Gross and Miss Ling, FDA inspectors, examined the Searle tests and found a number of discrepancies between the raw data and the summaries of the raw data submitted by the company to FDA on the drug, Flagyl.* For example, in the raw data, observations and notes were

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93/ The 1975-1978 Hearings on Drug Testing, Parts I-V (see Appendix A for full citations).

* Flagyl is indicated in the treatment of symptomatic trichomoniasis in females and in males (1979 Physicians' Desk Reference, p. 1595).

found regarding test animals which had died prior to the reported feedings. 94/ In the final report of the task force assigned to investigate the conduct of animal tests at Searle, the following conclusion was reached:

> At the heart of FDA's regulatory process is its ability to rely upon the integrity of the basic data submitted by sponsors of regulated products. Our investigation clearly demonstrates that, in the G.D. Searle Co., we have no basis for such reliance now * * *. We have noted that Searle has not submitted all the facts of experiments to FDA, retaining unto itself the unpermitted option of filtering, interpreting, and not submitting information which we would consider material to the safety evaluation of the product. 95/

FDA investigators felt the studies in question indicated carcinogenicity. Failure to report or incomplete reporting of such tests was the question here. Searle officials protested the conclusions of the task force, and maintained that the "deficiencies" were explainable, both scientifically and ethically, and that FDA and the task force had drawn conclusions without having all the facts. Their explanations of discrepancies and omissions included a computer error resulting in omission of data on tumor occurrence, which was corrected in other documents and materials; corrections made in subsequent submissions to FDA, which were a result of the pathologist reviewing the data a second time to catch any mistakes made the first time; and technical mistakes in gathering data--for example, inconsistently including the weight of the feed containers when weighing food administered to the test animals.

94/ The 1975-1978 Hearings on Drug Testing, Part I, pp. 52,63.

Flagyl was not the only drug manufactured by Searle that was scrutinized. Studies the drug Aldactone,* submitted to FDA in March 1975, indicated:

> Serious inconsistencies between raw data and summaries thereof, improper statistical manipulations of the data, improper execution of such studies, most of which have the effect of minimizing carcinogenic extent of the agent on test. 96/

A companion toxicity study on Aldactone was contracted by Searle to Hazelton Laboratories. The study at both laboratories reached the same conclusions regarding safety. Dr. Gross, however, who was involved in this case, doubted the validity of these conclusions:

> The main conclusion reached by both Hazelton and Searle from this particular study are that no problem on tumorigenesis or carcinogenesis for aldactone is evident. Our own conclusions on this study were twofold: (1) Its design and execution were so questionable, if not outright inadequate or faulty, that a conclusion on "safety" from a carcinogenesis point of view could not have been reached by reasonable reviewers; (2) despite the serious limitations to be placed on the reliability of this study from a "safety" point of view, we are confident that the study, questionable and unreliable as it was, nevertheless gave conclusive indications of tumorigenicity or carcinogenicity...The same tendency toward maximizing tumor detection for animals in the control groups while minimizing it for those exposed to the agent was evident also in this study...Far more serious is the failure to inform the computer that any malignant mammary tumors were found in the animals exposed to the agent. 97/

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* Aldactone is a specific pharmacologic antagonist of aldosterone, and is indicated in the treatment of a number of disorders, including primary hyperaldosteronism, edematous conditions, essential hypertension, and hypokalemia (1979 Physicians' Desk Reference, p. 1584).

96/ The 1975-1978 Hearings on Drug Testing, Part I, p. 64.

97/ Ibid.

Other companies besides Searle were also found to have submitted questionable data on animal tests. This usually meant that FDA suspected the omission of pertinent data. In 1975, three different companies manufacturing three different drugs — Practolol, a cardio-vascular drug; Slow-K, a potassium-chloride tablet; and Triflocin, a diuretic agent -- were suspected of criminal withholding of data or delay in reporting of crucial data. In each case, FDA's efforts to determine if criminal action occurred was interrupted by inaction, lack of commmunication, or loss of documents, all within the agency itself. 98/ In the case of Triflocin, manufactured by Lederle Laboratories, it was not a matter of the drug firm failing to submit relevant information to FDA, but rather the pathologists investigating the product failed to report their findings to the management expeditiously. After finally learning of the adverse effects revealed in the tests, firm officials promptly notified FDA, discontinued their studies of the drug, and recalled all unused supplies of Triflocin. 99/

During the mid-1970's, two private research laboratories came under scrutiny by FDA. An inspection of Biometric Testing, Inc. revealed several deficiencies, most of which were related to poor quality testing; but the inspection also revealed that some laboratory determinations alleged to have been carried out were not conducted at all. More

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98/ The 1975-1978 Hearings on Drug Testing, Part I, p. 43.

99/ Ibid., p. 137.

importantly, FDA inspectors found that on two occasions involving two different drugs and two different sponsors, pathology reports on a population of 70 test animals totally unrelated to the study were represented to the sponsor of the study, and then subsequently to FDA, as reports of animals treated with the test drugs. 100/ At the end of May 1979, a Federal grand jury in Newark, New Jersey returned an indictment accusing Biometric Testing, Inc. and officials of falsifying results of carcinogenicity tests on animals. This indictment is the first to lodge such charges against a private laboratory. 101/ Investigation of the second animal toxicology laboratory, Industrial Bio-Test Laboratory, also revealed deficiencies in test protocols and procedures, and resultant data were suspected of being manipulated. In one study, the occurrence of tumors was underreported by examining only a small number of the tumors which occurred and by inflating the number of total animals examined. 102/

Dr. Schmidt emphatically summarized the significance of this problem of reliable data in the following manner:

> I said earlier, and I said a number of times, that the bedrock of our decisionmaking process must be science, and that science must be without deceit. It must be impeccable. If we cannot rely on the scientific data that is given to us, then we cannot have a reliable decisionmaking process. The fact that in these particular instances, as Dr. Gross has pointed

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100/ The 1975-1978 Hearings on Drug Testing, Part III, p. 37.

101/ Mintz, Morton. Indictment Accuses Drug-Testing Firm of Falsifying Results. The Washington Post, June 1, 1979: A9.

102/ The 1975-1978 Hearings on Drug Testing, Part III. p. 728.

> out, we were aware of the studies and that our decisions about the drugs have been proper, in no way removes the fact that clearly confused and inadequate data were submitted to us. And this is and has been very alarming and disturbing to me. 103/

He went on to say that he felt there was actually more sloppy science than there was fraudulent science. Poorly controlled studies and recording practices are in one sense fraudulent, but they arise from negligence. When asked in 1975 how extensive this problem of unreliable data was throughout the industry, Dr. Schmidt replied that he did not know but planned to find out. 104/ A year later, Dr. Schmidt made the following statement:

> It is certainly more widespread than I would have guessed. I think it represents an area in which we have simply never been active in regulating, and now clearly we must be. 105/

He indicated that FDA was not the only Federal research agency on the receiving end of questionable data -- other agencies such as the Environmental Protection Agency and the National Cancer Institute also depend to varying degrees on submitted data in regulating or evaluating chemicals.

The DHEW Review Panel on New Drug Regulation indicated in their 1977 report that the falsification of data was not extensive throughout the industry. The Panel felt, however, that bias on the part of the

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103/ The 1975-1978 Hearings on Drug Testing, Part I, p. 67.

104/ Ibid., p. 68.

105/ The 1975-1978 Hearings on Drug Testing, Part III, p. 725.

drug sponsors was inevitable:

> While deliberate falsification of scientific data appears not to be a pervasive problem, all company-sponsored data are arguably subject to at least an unconscious bias based on the sponsor's natural desire to market a commercially successful product...For the most part, present safeguards against the submission of fraudulent test data appear inadequate to detect and minimize this type of bias. 106/

The distortion of data, whether it be inaccurate or misleading, has ethical implications regarding human testing. The Panel remarked that when test data do not accurately reflect the outcome of clinical trials, test subjects will have been exposed to the risks of an experimental drug without the possibility of a countervailing benefit. 107/

According to the Panel, however, several forces act to insure the promotion of reliable data. First, it is to the drug sponsor's benefit and financial interest to secure accurate information. Second, the professional ethic guides the conscientious drug investigator to develop reliable data. And third, legal action taken against criminal acts is a powerful incentive to drug firms to submit accurate information. 108/

Nevertheless, in spite of these safeguards, misleading and fraudulent data are occasionally submitted to FDA. In view of congressional testimony during the 1970s as well as during the 1968-1969 Nelson hearings, and as

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106/ Final Report of the Review Panel on New Drug Regulation, May 1977, pp. 84-85.

107/ Ibid., p. 83.

108/ Ibid., p. 84.

53-690 O - 79 - 6

reported by the Panel, this problem seems more serious with animal testing than with clinical testing. The Panel believed that this was due to the fact that animal testing is not as subject to peer scrutiny; and it is generally at the clinical stages when the results begin to be published in medical literature. There appears to be little, if any, oversight of the animal tests, even within the drug firms. For this reason, the Review Panel recommended that independent contractors "spot check" the results of a sample of animal tests and verify test results which appear questionable to FDA. 109/

The Panel pointed out that inaccurate data submissions might contribute to delayed approval since FDA would require that the sponsor conduct additional testing. A statement was recently presented at congressional hearings by Gregory Ahart, an official at the U.S. General Accounting Office (GAO). 110/ A GAO review of FDA's procedure for new drug approval was discussed in the statement. On the basis of GAO's analysis, the drug industry appears to have contributed to the long approval process by submitting incomplete drug applications and not giving high priority to correcting deficiencies identified by FDA. 111/ Three out of twenty unapproved NDAs followed up by GAO were incomplete. Two of the sponsors

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109/ Final Report of the Review Panel on New Drug Regulation, p. 86.

110/ Ahart, Gregory J. The Food and Drug Administration's Drug Approval Process. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology, (unpublished). June 19, 1979.

111/ Ibid., p. 8.

of these products indicated that they had been unaware of what FDA wanted. 112/ The requirement proposed in pending legislation (96th Congress, S. 1075) that FDA issue guidelines on preclinical and clinical testing might be the answer to problems such as this.

112/ Testimony of Gregory Ahart, June 19, 1979, pp. 12-13.

VI. "THIRD PARTY" TESTING/SURVEILLANCE

A. 1968-1969 Hearings

The suggestion of bias on the part of manufacturers and investigators was repeatedly mentioned in the 1968-1969 hearings, and the development of a third party system was felt to be the answer by minimizing this inherent potential for bias. Suggestions ranged from the creation of an independent agency to no outside source at all, but rather increased firm monitoring of their own studies; several suggestions fell between these two extremes. It appeared that most, if not all, of the contributors to the hearings on drug testing had comments on this idea, including: Dr. Paul Lowinger, Dr. A. Dale Console, a committee of the Alabama Medical Association, Dr. Herbert Ley, the Council of Health Organizations, and Dr. Franz Inglefinger.

One of Dr. Lowinger's chief complaints as a drug investigator was that investigators were often denied access to scientific information already known about the drug they were about to test in humans, added to which investigators are generally unaware of others' work on the same product. It was noted that the National Institutes of Health (NIH) annually published a listing of NIH-supported research projects and which researchers were conducting them. Dr. Lowinger envisioned a separate Federal agency or institute, supported by the Federal Government and/or the pharmaceutical industry, but separate from FDA. This institute's primary function would be to supervise drug research, with an emphasis on new drug clinical investigation. It would provide a scientific

capability with any of a number of possible roles--the funding of drug investigations, the oversight of drug trials, or the actual carrying out of the drug testing. The implication was that this institute would also coordinate research, enabling investigators of the same product to exchange ideas and pool information for analysis and clarification. Such a system would also serve to minimize duplicate testing involving humans. Approval of drugs would also rest with the new agency. Investigators would be required to send regular summary reports and a final report to the new agency, as opposed to the present system where researchers send their results to the drug sponsors. 113/

Dr. Console also supported the idea of a central agency. Like Dr. Lowinger, he felt such an agency should be jointly supported by Federal funds and by fees paid by drug firms. The preservation of anonymity between the drug sponsor and the investigator, and the selection of investigators based largely on qualification, would be the two major benefits of the agency. When asked what he felt about Dr. Lowinger's statement that an investigator should know who other researchers are and the results of their work, Dr. Console replied:

> In any kind of large scale research, proper coordination of the research is almost as important as the research itself. My suggestion that a central agency act as an impartial intermediary between the drug company and the investigators was predicated on the assumption that the central agency would serve as a coordinator. So long as rights regarding publication are respected, failure to follow Dr. Lowinger's suggestion would be foolish. 114/

113/ The 1968-1969 Hearings on Drug Testing, vol. 10, pp. 3997-4008.

114/ Ibid., vol. 11, p. 4488.

As discussed earlier in this report, the Alabama Medical Association appointed a committee to examine the issue of Dr. Stough's drug tests in the Alabama prison system. The Alabama Committee's comprehensive report included analytical comment on the "third party" concept, much of which resulted from their comparison of the Alabama system with control measures taken in other States. It was found that "human use" committees and "human experiment review boards" provided adequate supervision of drug tests involving prisoners. 115/ The report variously referred to this "outside source" concept as an agency, professional committees, officially designated commission, regulatory boards, and a State foundation. 116/ The commissions/committees/boards are comparable to a general monitoring system, making use of peer review. The suggestion of the Alabama Committee, especially for the State of Alabama, was to establish a foundation under a State institution (possibly Auburn University) which would be responsible for "reviewing all protocols from pharmaceutical firms, or others submitting clinical research projects, assessing hazards inherent in the projects and critically evaluating the safeguards to be provided." 117/ Such a foundation would in most cases also be asked to undertake the research set forth in the protocols.

115/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5695.

116/ Ibid., pp. 5889-5702.

117/ Ibid., p. 5698.

Dr. Ley exhibited strong support for the development of peer review committees, established under FDA regulation. In testimony before the subcommittee, he made the following comments:

> This area--that is, investigational drug testing in man--is the only area in medical research funded by or overseen by the Federal Government that does not have the requirement for a peer review committee today. I think it is time that such a committee be established. 118/

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> It came rather forcibly to the attention of both my staff and myself during the review of the Stough incident and also in preparation for this testimony that there was an important gap in the protection of the patient or the subject which did not have the peer group working to review and to evaluate the conditions under which the experiment studies were done. 119/

Dr. Ley felt that a system such as this would satisfy the need for clinical test monitoring and would be an intermediate solution between two extremes.

Regarding Senator Nelson's question of an "independent source" serving to eliminate bias, Commissioner Ley responded with this:

> I know this concept has been presented on several occasions to your committee. Theoretically, I grant that the introduction of an unbiased, dispassionate evaluator could possibly contribute to the drug testing system. On the other hand, I would also say that another answer that might be equally acceptable would be for the drug sponsor to conduct his monitoring operations more effectively and more objectively... 120/

118/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5664.

119/ Ibid., p. 5666.

At the time of Dr. Ley's testimony in 1969, FDA had already prepared a proposal making all investigational studies conducted in Phase 1 or Phase 2 trials, and those Phase 3 studies taking place in institutional settings, subject to review by a peer group committee. Such committees would operate on a continuing basis, not simply for initial approval of a study, to assure sound and scientifically justified results. 121/ The peer groups would be appointed by the institutions where the tests are being conducted (such as medical schools, teaching hospitals, and prisons), and it would be their responsibility to oversee the execution of protocols, and to insure that human subjects were being protected and informed consent given. Unfortunately, such a system would not cover those investigators without a peer group, such as the individual physician researcher. It was recognized that this system itself would require some oversight so that all review committees worked under similar guidelines.

A statement by the Council of Health Organizations was submitted to the subcommittee as supplemental material in direct response to Dr. Ley's testimony. The Council supported the basic premise of the FDA proposal for peer review, but held specific reservations about the actual formulation of the proposal:

> Some outside group, independent of the investigator and the new drug sponsor, is needed to protect the rights and safety of human test populations. The FDA has proposed that "peer review committees" be established

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121/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5664.

> to function as an independent reviewing body. We agree that much good could be accomplished by an experienced, independent review committee operating under a clear mandate to safeguard the test subjects' rights, safety, and welfare. Yet the FDA proposal would not establish such groups. 122/

The Council's basic objection was that, even though the proposal was patterned after the already established Public Health Service/National Institutes of Health peer groups, the FDA proposal failed to include the provisions which would assure the effectiveness and independence of the peer groups. The Council also felt that the proposal did not address the problem of adapting the peer group concept to institutions such as prisons and orphanages as it did to hospitals and university settings. 123/ Other criticisms included the undefined responsibilities and authority of the review committees, and the limitation of the coverage to only Phase 1 and Phase 2 tests in institutional settings. Among other suggestions, the Council proposed the following: 124/

> -- that FDA develop a plan to formulate a long-range strategy to assure the welfare of test subjects, and appropriate guarantee of scientific necessity and adequacy of new drug testing;
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> -- that, in developing this strategy, FDA solicit the opinion of public groups - consumer, patient, health care groups - as well as drug manufacturers and investigators; and
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> -- that FDA consider other approaches less oriented to individual institutions, such as FDA itself setting up regional panels to oversee and review the testing of new drugs.

122/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5717.

123/ Ibid.

124/ Ibid., pp. 5717-5718.

Dr. Inglefinger presented his views on the independent "third party" concept in his 1968 testimony. Assuming that a central agency were to be established to arrange the testing of drugs, he felt such an organization should be multi-partisan, representing the medical profession and the pharmaceutical industry, as well as Government interests. A cooperative effort such as this would be essential if it were to be accepted by all the parties involved. Dr. Inglefinger believed, however, that the benefits of this agency -- increased objectivity and the trustworthiness of drug testing procedures so attained -- must be weighed against the costs in time and money that would be entailed in implementing it. While admitting that such a system would reduce bias, he expressed doubts as to whether or not anonymity between the investigators and the drug firms could really be maintained. Without discounting the potential advantages of an independent agency, Dr. Inglefinger clearly was not convinced that this would be the ideal solution:

> ...it seems to me that it would be more direct if drug firms tried to make their own arrangements with universities, to have drugs studied rather than having an intermediate agency, which in its arrangements with investigators would unavoidably introduce delays...perhaps some honor system, such as the NIH had established with various medical schools, could be initiated, with the individual universities assuming responsibility for the trustworthiness of drug studies carried out by their staffs. 125/

125/ The 1968-1969 Hearings on Drug Testing, vol. 10, p. 4025.

B. 1969-1979

Interest in the development of an independent third party for testing and/or monitoring drug studies remained strong in the 1970's. In 1971, requirements were established for "institutional review committees." 126/ Committee members include lawyers, clergymen, laymen, and scientists, and are appointed by the institutions where drug tests are being conducted, such as hospitals, prisons, research facilities, and so forth. FDA inspects the institutions periodically to determine if the committees are operating properly. The responsibilities of these committees include regular monitoring of the tests under their purview, assuring that protocols are being followed, and insuring that the rights and health of the test subjects are being upheld. FDA reviewed the use of inmates in 19 prisons, and found that abuses had clearly occurred. They determined that many of the shortcomings were related to deficiencies in the operation of the review committees, with defects in consent forms and procedures being common. 127/ In some instances, they found that review committees were not operational at all. The major limitation of these regulations is that they cover only institutionalized subjects. In 1975, FDA Commissioner Schmidt stated that local review committees would have a more general applicability. At that time, however, FDA had not yet formulated a workable method to include all research subjects. 128/

126/ The 1975-1978 Hearings on Drug Testing, Part I, p. 146.

127/ Ibid., p. 50.

128/ Ibid., pp. 79-80.

In spite of the requirements for institutional review committees, primary responsibility for overseeing drug tests still lies with the drug industry. Dr. Schmidt stated that:

> The principal responsibility...for monitoring clinical investigation rests with those doing it on a professional basis first, that is, the investigator, and, second, with the sponsors of the IND or the NDA, so that the principal responsibility has been and really must be with the industry. 129/

FDA monitors drug tests to a limited extent, as described earlier. They generally investigate particular investigators and studies "for cause." Spokesmen for FDA have repeatedly said since 1968-69 that the agency intends to expand its inspections of animal laboratories and its surveillance of clinical investigators.

The final report of the DHEW Review Panel on New Drug Regulation reported that while development of FDA guidelines would do much toward improving the quality of drug tests, such guidelines would be ineffective without careful agency monitoring of the studies. 130/ The Panel further concluded that their suggestion of "spot checking" animal tests would be preferable to having all preclinical testing conducted by an independent third party. They felt that third party testing might stifle drug innovation since drug development is closely tied to the basic animal testing. 131/ Clinical testing by a sponsor-independent party, however,

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129/ The 1975-1978 Hearings on Drug Testing, Part I, p. 9.

130/ Final Report of the Review Panel on New Drug Regulation, May 1977, p. 71.

131/ Ibid., p. 87.

was considered a good idea. The Panel suggested three ways in which this might be accomplished -- limited third party testing, complete Government testing, or Government contract of testing. 132/

Limited third party testing would have its disadvantages, according to the Panel's report; human subjects would be subjected to duplicative testing since drug firms would still sponsor their own tests, and the establishment of such a system would be difficult, costly, and time-consuming. 133/ Total Government testing would require that the Government evaluate the results of its own tests, but would eliminate industry bias in reporting results. Independent contracting would also eliminate the bias, and furthermore, it would constitute less regulatory intrusion into the drug industry process. 134/

Dr. Sidney Wolfe, director of the Public Citizen Health Research Group, feels that since testing is the major problem in industry's development of drugs, this is what should be removed from the industry and placed with independent third party testers. 135/ These testers would not be obligated to or dependent upon the drug firms, and thus should not feel inclined to obtain results which would "please" the drugs' sponsors.

132/ Final Report of the Review Panel on New Drug Regulation, May 1977, p. 88.

133/ Ibid.

134/ Ibid., p. 89.

135/ Wolfe, Sidney (interview with). Drugs: A Consumer Advocate's View. FDA Consumer, vol. 12, December 1978-January 1979: 13.

Proposed legislation currently under consideration in the 96th Congress has incorporated the concept of a new agency acting as a third party. This idea is in line with the suggestion made by Dr. Paul Lowinger in Senator Nelson's 1968 hearings. On March 27, 1979, Senator Nelson introduced a bill (S. 774) which would establish as part of FDA a National Drug Testing and Evaluation Center. This Center would make DHEW responsible for both testing and evaluating drugs. On May 3rd, Senator Edward Kennedy introduced the "Drug Regulation Reform Act of 1979" (S. 1075). Title XVIII of that Act would establish a National Center for Drug Science. This Center would conduct and support drug research; conduct drug science policy research; conduct continuing review and analysis of the use of drugs in the U.S.; and make grants and support training programs in clinical pharmacology.

VII. HUMAN TEST SUBJECTS

A. History

Efforts aimed at protecting human subjects in medical experiments date back many years. In 1948, the Nuremberg military tribunals developed a ten-point code regarding the use of humans in clinical research. The ten points are concerned with the purpose and quality of the experiments and the protection of the human test subjects [see Appendix B]. This code was issued in response to the horrors which occurred in Nazi death camps.

Fourteen years later, the United States took its first step in legislating the protection of test subjects. The 1962 Amendments to the Food, Drug, and Cosmetic Act required that subjects be informed as to the nature of the test, and that consent be obtained.

In 1964, the World Medical Association met in Helsinki, Finland to discuss the importance of human rights in experimentation. The result of this meeting was the issuance of "The Declaration of Helsinki" which set forth specific standards for research on humans. The document specifically noted that consent, preferably written, should be obtained from relatives or legal guardians if the patient was incapable of rendering it. 136/

Deficiencies in official regulation of human experimentation became apparent, and subsequent efforts have been made to strengthen requirements for the protection of human subjects.

136/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5712.

B. 1968-1969 Hearings

At the time of the 1969 hearings, FDA had two major responsibilities concerning drug testing: 1) protecting the public from dangerous and ineffective drugs, and 2) protecting human subjects in new drug testing. The two duties create a great deal of tension in that it is often difficult to satisfy both needs at the same time, or to address one without compromising the other. The protection of human subjects is by no means limited solely to drug testing. It is however, one of the major concerns in the drug testing issue, and was specifically addressed in testimony and supplemental materials presented in hearings on August 12, 1969.

Dr. Herbert Ley, then Commissioner of Food and Drugs, told the subcommittee that two basic principles existed to protect the subjects of clinical trials -- 1) there should be adequate indication in IND applications that animal tests have provided enough information to demonstrate that experiment in man is justified, and 2) investigators should be competent, concerned, and qualified to recognize drug effects and treat adverse reactions. 137/ To further assure that the rights of the subjects are protected, FDA promulgated regulations defining the requirements of informed consent. 138/

The case of Dr. Stough's drug testing prrogram in the Alabama prison system, discussed at length during the hearings and summarized earlier in this report, exemplifies the direct relationship between the quality of the testing and the protection of the subjects. Thus, many of the

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137/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5643.

138/ 21 CFR 310.102.

criticisms on Dr. Stough's handling of the tests also indicated failings in the protection of his test subjects. The Committee appointed by the Alabama Medical Association to examine the case made the following statement at the beginning of their report:

> It is also RIGHT that every precaution be taken to safeguard the health of the prison inmates. We believe that this has been done in principle and in policy but that under the existing circumstances, it has not been possible to do so in detail. 139/

Deficiencies affecting the welfare of the subjects included: insufficient explanation of the tests and possible side-effects; inadequate supervision by trained personnel; questionable physical examinations; untrained personnel carrying out medical duties; poor medical facilities; the unique pressure toward signing a "consent form" because of payment for participation 140/; and the lack of adequate review over test protocols. While most of these deficiencies were evident at one or two prisons in particular, the Alabama Committee noted a high quality of testing and patient care at another prison in Alabama. They stated that prison officials knew what was going on and had details of each protocol in front of them. The test subjects were well informed and reported regular and adequate supervison. In fact, the testing program had provided a means whereby previously undetected illness was identified in some prisoners. 141/

139/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5689.

140/ Prisoners were paid $1 for each day they participated in a study.

141/ The 1968-1969 Hearings on Drug Testing, vol 14, pp. 5691-5692.

The Committee reported that the Alabama Board of Corrections had assumed that any physician conducting tests on human subjects would take all precautions to insure the health of these people. One statement in the Committee's report regarding the placement of responsibility for the protection of subjects elicited a protest from Dr. Ley; both the statement and Dr. Ley's response follow:

> COMMITTEE REPORT: It should be noted, however, that neither [the drug firms nor the FDA] is primarily concerned with the rights and welfare of the institutionalized research subject. There is within the body of the law some provision for protecting the welfare and rights of prisoners used as research subjects, but in the absence of sufficient funds and some watchdog mechanism, these rights may be abused. There is the justifiable view that the drug manufacturer is not abandoning any moral or ethical responsibility in assuming that the welfare of institutionalized human subjects used in testing its products will be adequately underwritten by the administrators of the institutions or by other state agencies, boards, or commmissions charged with that responsibility. 142/
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> DR. LEY: The Federal Food, Drug, and Cosmetic Act under Section 505(i) and Section 130.3 of the New Drug Regulations place a definite and primary responsibility on both the FDA and the sponsor of an investigational study to assure that the health of the participants in such a study is protected. The sponsor must be sure that he selects capable investigators who can safeguard the subjects of the study, that adequate preclinical tests demonstrate that administration of the drug to man is justified, that there is a sound plan of testing (protocol)

142/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5695.

> which minimizes risks to the subjects, that unexpected effects are promptly investigated and the study is stopped if they raise significant safety questions, and that each investigator agrees to obtain the consent of the subjects of the experiment...The FDA in reviewing the submissions sponsors must make before initiating clinical trials, is required to assure itself that sponsors have met the above-mentioned requirements, as well as others, and to require cessation of the trials where appropriate safeguards are not observed. 143/

In comparing the Alabama system with those in other States, the Alabama Committee found that where review boards or committees existed to oversee such clinical tests, the subjects' welfare was very adequately protected. While recognizing that such review groups were not available in the Alabama incident, the Committee nevertheless felt that existing individual responsibilities were not upheld:

> There were insufficient controls over drug programs in allowing Dr. Stough a free hand within the prison system. The responsibility for this omission of controls to protect the prisoners must rest by virtue of their authority ultimately on the Board of Corrections. 144/

A report submitted to the subcommittee by the Council of Health Organizations described abuses in drug tests. The Council felt that the welfare and safety of test subjects has never been adequately insured, and that certain groups are particularly vulnerable to testing abuse:

> ...problems are most acute in tests involving the poor, the dispossessed, and the helpless. Since few people are anxious to participate in

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143/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5679.

144/ Ibid., p. 5697.

> medical experiments, drug investigators understandably make heavy use of those people least able to resist the investigator's request. Such people are especially valuable to the investigator when they can be tested and observed in institutionalized settings such as orphanages, prisons, mental hospitals, and homes for the elderly. 145/

Like Dr. Ley, the Council believed that "peer group committees" could do much to improve the test subject's situation by increasing oversight and review of the tests. But as the FDA proposal was first written, the Council objected to many features or omissions, including the fact that it did not address itself to the problems of establishing the peer group concept in institutions such as prisons, orphanages, or homes for the aged. They also felt that the proposal did not adequately and clearly define the responsibilities of the review committees regarding the protection of subjects. Besides assuring the rights and welfare of test subjects, the Council felt it should also be the committees' responsibility to assure that methods used to obtain informed consent were adequate and appropriate, and that the risks to the individual were outweighed by potential benefit to him or by the importance of acquired knowledge. 146/ In the matter of obtaining consent from less competent groups of people, the Council made the following suggestion:

> ...obtaining the consent of children in orphanages and the senile in homes for the elderly is a delicate matter at best. Often

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145/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5717.

146/ Ibid., p. 5720.

> their legal guardian is the state. Members of such groups would benefit from a review committee acting in their interest to make sure that the state safeguards their rights. 147/

During testimony, Dr. Ley addressed the question of obtaining consent from the elderly and children. Recognizing the difficulty of this question and the continuing controversy over it at the time of the hearings, Dr. Ley and his counsel ventured to say that legal guardians, relatives, or even superintendents of institutions may be able to grant consent depending on State laws. 148/ Mr. Benjamin Gordon, counsel to the subcommittee, presented news articles citing cases where elderly and mentally retarded groups of people were subjected to tests [not all drug tests]. Whether or not consent was given was questionable; and again it appeared from the articles that it was unclear exactly who was responsible for monitoring such trials. 149/ Dr. Ley responded that the peer review system, as utilized by the Public Health Service, had done much to modify such circumstances. He went on to say that FDA was responsible for one of the studies mentioned, and that informed consent was obtained from every subject in that particular study. 150/

It was apparent that the issue of human experimentation was a concern at both congressional hearings and in the public media in 1969. This interest presaged a burst of activity in the 1970s regarding the protection of human test subjects.

147/ The 1968-1969 Hearings on Drug Testing, vol. 14, p. 5720.

148/ Ibid., p. 5710.

149/ Ibid., pp. 5709-5711.

150/ Ibid., p. 5711.

C. 1969-1979

Rapid advances in drug development and other biomedical research fields have resulted in the increasing need for and use of human subjects in clinical testing. Particularly in the 1970s, human experimentation has become a separate issue of great concern. Much has been written on this subject, and definitive steps have been taken to assure that the rights and health of human subjects are protected. Informed consent, selected test populations, and adequate medical supervision of test subjects have been issues of particular concern in the area of drug testing in humans.

The right of the public to receive only safe and effective drugs must be balanced against the rights of the test subjects who are so necessary to the drug development process. To this end, there have been numerous efforts to improve clinical testing without compromising the high standards of safety and efficacy in drug development. It has been pointed out earlier in this report that poor quality testing and faulty or incomplete data endanger the public and raise ethical questions concerning the risks taken by test subjects without the possibility for countervailing benefit.

In the later stages of clinical testing, a drug is tested in patients suffering from the condition for which the drug is intended. These tests generally involve one group receiving the new drug and another group(s) receiving either placebos (medically inert substances) or other products already on the market. At some point, if the new drug shows effectiveness, another ethical question arises -- how long can the patients in the control groups be denied a potentially beneficial or even life-saving drug?

Another major consideration in the use of humans for drug testing, and one which has remained controversial, is the question of who participates in these trials. Critics claim that the drug development system makes use of "captive audiences" -- prisoners and other institutionalized people such as the elderly and the retarded. There is also the impression that the poor and racial minorities participate in these trials in disproportionate numbers. Dr. Schmidt, the Commissioner of FDA in 1975, testified that to the best of his knowledge, test populations such as the aged, the very young, or the mentally ill, are used only in testing drugs applicable specifically to these groups, and only when the patients require treatment. 151/ This brings up the distinction that needs to be made between therapeutic versus non-therapeutic studies. In early studies, the drug is non-therapeutically tested in normal, healthy subjects, to ascertain the action of the drug and its pharmacologic properties. Therapeutic studies are those in which the drug is given to patients affected by a condition for which the drug is intended, to determine how the drug acts on the disease or condition. The majority of subjects in the early non-therapeutic trials are prisoners. An FDA review of eleven NDAs found no instance in which Phase 1 trials were conducted with retarded individuals, mental patients, or children. 152/ In Phases 2 and 3, appropriate patient populations

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151/ The 1975-1978 Hearings on Drug Testing, Part I, p. 49.

152/ Ibid., p. 99.

were used:

> ...children were studied in trials for a drug to treat hyperactivity, mental patients were studied in trials of antipsychotic drugs, and elderly patients were studied mainly in trials for Parkinson's disease. 153/

Congressional subcommittees 154/ in 1975 heard testimony from a panel of drug company officials representing seven prominent pharmaceutical firms. These officials substantiated Dr. Schmidt's remarks. Each witness described the population groups used by his respective firm. In general, Phase 1 studies were conducted in affiliated community hospitals and clinics or in the firms' own clinics. Most used prison populations to varying degrees; and most of these studies were conducted at the firms' own clinics or at the prisons. One witness stated that while his firm did use prisoners, an increasing number of volunteers, students, and firm employees were being used. Later testing usually involved populations from universities, teaching hospitals, and hospital research centers. Specific groups such as the aged and the mentally retarded were used only occasionally and only for specific drugs aimed at those groups. Phase 3 studies often involved practitioners in the community administering the drug in a community population. 155/

153/ The 1975-1978 Hearings on Drug Testing, Part I, p. 99.

154/ (Senate Committee on Labor and Public Welfare, Subcommittee on on Health; and Committee on the Judiciary, Subcommittee on Administrative Practice and Procedure).

155/ The 1975-1978 Hearings on Drug Testing, Part I, pp. 381-385.

Prisoners are probably the most vulnerable to potential abuse. Instances of such abuse usually relate to ineffective review boards, poor medical care and supervision, and improper informed consent procedures. These abuses, of course, can occur in non-prison situations, too. The advantages of prison testing are obvious: the group is confined; test conditions are usually stable, controllable, and easily identified; and observation and follow-up can be easily achieved. In a prepared statement, Dr. Schmidt said that the same advantages that are available in prison populations could be obtained in other populations such as college students or paid volunteers, but at considerable cost and effort. 156/

It should be noted here that the pay prisoners receive for their participation in drug tests is a powerful incentive; this fact alone raises ethical questions concerning the voluntary nature of participation, adequate informed consent, and possible coercion. Congressional hearings in the 1970s, special study groups, and published literature have examined the ethics of prison testing and abuses which have occurred. In view of these concerns, and in spite of the advantages of prison testing, some States have forbidden such testing in the their prison populations. 157/ During the 1975 hearings, Senator Edward Kennedy made the following statement in this regard:

> We are not claiming all prison testing is slipshod. However, the trend in the Nation is clearly toward the elimination of prison testing on a State-by-State basis. 158/

156/ The 1975-1978 Hearings on Drug Testing, Part I, p. 100.

157/ Ibid., p. 101.

In February 1975, the Pharmaceutical Manufacturers Association (PMA) approved a set of guidelines on the use of prison inmates in clinical drug research. "'Since it is the industry's conviction that research conducted in the controlled environment of correctional institutions if of vital importance to the progress of medicine'. . . the industry must act to ensure that company-sponsored prison testing is 'consistent with the best standards of science, ethics and law.'" 159/ These guidelines attempt to address the problems concerned with prison testing and include requirements pertaining to facilities, medical care, the rights of the prisoners, informed consent, and independent institutional review committees. In July 1975, PMA issued a report outlining its policy on clinical research. A large portion of this document was devoted to the rights of human subjects in clinical drug investigations. 160/ This section examines the elements in human testing necessary to protect the test subjects.

Testing drugs in pregnant women and in children is a delicate and complex issue. These groups also need the benefit of safe and effective drugs, but to adequately evaluate the use of drugs in these groups requires that testing be done on them. Most drugs are not tested in pregnant women and labeling is required to indicate this; extensive testing in pregnant animals, however, is required. FDA believes that drugs should

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159/ PMA Board Adopts Guidelines on Clinical Drug Trials in Prisons. Washington Drug & Device Letter, February 24, 1975: 2.

160/ The 1975-1978 Hearings on Drug Testing, Part I, pp. 338-359.

be tested in children, but only under carefully controlled circumstances. 161/

As mentioned earlier, the protection of human subjects of biomedical research became a separate issue in the 1970s. The Federal Government initiated action in 1969 when the Department of Health, Education, and Welfare (DHEW) established guidelines for the protection of human research subjects. These regulations were subsequently revised in 1971, 1974, and 1975. In 1978, DHEW proposed regulations regarding the use of prisoners and children as research subjects.

In 1974, Congress passed the National Research Act, (P.L. 93-348), which contained a title concerned with the protection of human subjects. (Title II established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.) The duties of the Commission were to identify basic ethical principles and develop appropriate guidelines for the conduct of biomedical and behavioral research involving human subjects. Further, the Commission was directed to examine specific issues, including the use of children, prisoners, and mental patients as research subjects, and the practice of informed consent. During its existence, the Commission published several reports and recommendations on specific subjects, including the use of prisoners, the use of children, and the establishment of institutional review boards, to name only a few. 162/ The U.S. Code of Federal Regulations, (45 CFR 46), contains the accumulated regulations

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161/ Pines, Wayne L. A Primer on New Drug Development. FDA Consumer, vol. 8, February 1974: 18.

162/ Some of the Commission's reports are included in the selected bibliography appended to this report. For a more complete listing of references on the issue of human research subjects, refer to the Library of Congress "issue brief" (IB 74095), prepared by the Congressional Research Service (July 23, 1977; updated July 17, 1979).

on human subjects and has incorporated recommendations of the National Commission.

The National Commission's term expired on November 1, 1978. On November 9, 1978, legislation was enacted (P.L. 95-622) which contained a Title III establishing "The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behaviroal Research." This Commission will have a broader focus than that of the previous National Commission.

Over the past decade, a code of regulations regarding the protection of human research subjects has been evolving. A large part of these regulations concerns informed consent. Consent is generally required except when consent is not feasible or when the physician determines that it is not in the best interest of the patient. Consent for drug investigation in Phases 1 and 2 must be in writing. 163/ Presently, informed consent is required only for the testing of drugs prior to approval by FDA; it is not officially required in clinical testing conducted after the approval of a drug. The DHEW Review Panel on New Drug Regulation concluded that FDA should be able to require a sponsor to obtain informed consent from test subjects when further testing is undertaken after approval. 164/

163/ U.S. Department of Health, Education, and Welfare. Food and Drug Administration. Clinical Testing for Safe and Effective Drugs. [DHEW Publication No. (FDA) 74-3015] p. 3.

164/ Interim Report of the Review Panel on New Drug Regulation, April 25, 1977, p. 17.

In addition to specific regulations on the use of human research subjects and informed consent, other requirements in the drug regulatory system are significant. Requirements for animal testing, sponsors and monitors, clinical investigators, and institutional review all are designed to minimize the risks involved with testing new drugs and to assure that investigational subjects are fully informed of these risks.

On August 14, 1979, regulations were proposed in the Federal Register (volume 44, Tuesday, August 14, 1979, pp. 47688-47712) to amend basic HEW policy for the protection of human research subjects, and to implement new regulations concerning FDA standards for Institutional Review Boards for Clinical Investigations. Both proposals are in response to the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research concerning institutional review boards.

VIII. LEGISLATION

A. History

The legislative role of the Federal Government in controlling drug products to assure the safety of the public dates back to 1848. For the most part, the National Drug Import Law of 1848 and all subsequent legislation are limited to drugs in interstate commerce. Any drug product manufactured and distributed or used within the boundaries of a State would come under the jurisdiction of State authorities and regulations.

The succession of drug acts and amendments illustrates Government's increasing involvement in drug regulation. Modifications of earlier acts were designed to enhance quality control and further insure the interests of the public. A chronological summary of drug-related legislation follows: *

1848 - The National Drug Import Law was enacted on June 26, 1848. This was an act designed to prevent the importation of "adulterated and spurious" drugs and medicines. The Act authorized and required the Secretary of the Treasury to appoint qualified persons as special examiners of drugs, medicines, chemicals, etc., at various ports.

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* These acts generally include several aspects of drug control, such as labeling, manufacturing, packaging, advertising, and so on. These "summaries", however, include only those provision which have some bearing on drug testing and evaluation.

1906 - Enacted in 1906, the purpose of the Pure Food [and Drug] Act was to prevent the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes. The Act made it unlawful to manufacture or ship in interstate commerce any adulterated drug. It also provided that "examinations of specimens of foods and drugs shall be made in the Bureau of Chemistry of the Department of Agriculture, or under the direction and supervision of such Bureau, for the purpose of determining from such examinations whether such articles are adulterated or misbranded within the meaning of this Act..." Misbranded here referred to false or misleading information on the package or label, concerning the product or the ingredients or substances contained in the product.

1912 - The Sherley Amendment changed the 1906 Act by adding that false and fraudulent information on the package label of a drug would also cause the product to be "misbranded." The intent of this legislation was to prevent companies from making false and fraudulent claims on the curative or therapeutic effects of the drug.

At this point it was recognized that the poor manufacturing techniques and the absence of quality control were still causing problems in spite of

the enacted legislation. Consequently, FDA, collaborating with the pharmaceutical industry began developing assay techniques and standards. There was still no Federal requirement that a drug be proved safe before marketing -- only that it meet the standards set forth in the United States Pharmacopeia or The National Formulary.*

1938 - The Federal Food, Drug, and Cosmetic Act of 1938 was the first piece of legislation requiring that safety be shown for each new drug. The Act required that an application [presently known as a New Drug Application (NDA)] be submitted to FDA by the sponsoring firm and that it meet certain requirements before being introduced into interstate commerce. In regard to drug testing, the application must include "...full reports of investigations which have been made to show whether or not such drug is safe for use..."

> ...sec. 505(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in

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* The U.S. Pharmacopeia (USP) and The National Formulary (NF) are two of the official compendia recognized by the Food, Drug, and Cosmetic Act [Sec. 201(j) FD&C Act]. The law designates these compendia as the sources of standards for strength, quality, and purity of medicinal products sold in interstate commerce. In 1974, at a convention of USP and NF officials, an agreement was reached by both parties to consolidate the two compendia and publish one U.S. Pharmacopeia in 1980.

> the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is unsafe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions, he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.
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> (e) The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds (1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective, or (2) that the application contains any untrue statement of a material fact...
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> ...(i) The Secretary shall promulgate regulations for exempting from the operation of this section drugs intended solely for investigational use by experts qualified by scientific training and expertise to investigate the safety of drugs. 165/

At this time, then, drugs were required to meet two basic standards:

1) proper labeling and 2) safety. In 1962, amendments were enacted which added efficacy to the criteria new drugs must meet.

1962 - The Drug Amendments of 1962, often referred to as the Kefauver-Harris Amendments, elaborated upon the safety

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165/ The Food, Drug, and Cosmetic Act of 1938.

standard provided for in earlier acts, and added a requirement to prove efficacy:

> sec. 505(d) . . . (5) evaluated on the basis of information submitted to him [the Secretary of DHEW] as part of the application and any other information before him with respect to such drug, [if] there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof... he shall issue an order refusing to approve the application. 166/

In addition to proving efficacy for new drugs, the Act required that drugs marketed between 1938 and 1962 had to be evaluated for efficacy. 167/ The Act further provided that approval of applications may be suspended if new tests, clinical experiences, or newly disclosed information shows lack of safety; or, if on the basis of new information, insufficient evidence exists to support the claims of efficacy; or if the applicant has failed to establish a system for maintaining required records; or if the applicant has refused to permit access to, or copying or verification of, such records. The exemption from the requirements demanded for new drug application, as stated in sec. 505(i) quoted earlier from the 1938 Act for drugs intended only for investigational use, was detailed in the 1962 Amendments.

166/ The Drug Amendments of 1962, P.L. 87-781.

167/ This task was eventually contracted by FDA to the National Academy of of Sciences/National Research Council which submitted final reports between 1967 and 1969.

The investigational new drug application [IND] requirements highlighted the issue of informed consent. To insure the rights of human subjects who were being used for the clinical testing of a new drug, the 1962 Act required that the subjects be informed that the drug was investigational, and required that consent be obtained:

> Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgement, contrary to the best interests of such human beings. 168/

In addition to the Food, Drug, and Cosmetic Act and its subsequent amendments (U.S.C., Title 21, Chapter 9), another section of the United States Code provides the authority under which charges can be brought against offenders for supplying the Federal Government with false or fraudulent information. In action initiated by FDA, drug sponsors and investigators have been formally charged under this provision:

> Chapter 47 - Fraud And False Statements
> sec. 1001. Statements or entries generally.
> Whoever, in any matter within the jurisdiction

168/ The Drug Amendments of 1962, P.L. 87-781.

of any department or agency of the United States knowingly and willingly falsifies, conceals or covers up by any trick, scheme, or device a material fact, or makes any false, fictitious or fraudulent statement or representations, or makes or uses any false writing or document knowing the same to contain any false, fictitious or fraudulent statement or entry shall be fined not more than $10,000 or imprisonment not more than five years, or both. 169/

With the implementation of the 1962 Amendments, and the resultant regulation, Federal control over drug development and approval was greatly increased. The Kefauver-Harris Amendments were the last major legislative revisions enacted on drug regulation. The pharmaceutical industry has repeatedly expressed its displeasure with the existing legislation, and has found it difficult to comply with the regulations without adversely affecting drug innovation.

Unlike the 1938 and 1962 Acts, which were initiated in response to drug tragedies [sulfanilamide poisoning in the case of the 1938 Act and thalidomide in 1962], recent legislative proposals represent forty years of drug experience, increasing consumer awareness, and intense investigations by congressional committees.

B. Proposed Legislation

After 1962, it soon became apparent that existing drug legislation still did not satisfy the needs of the drug industry, the Food and Drug Admininstration, or the public. Drug industry officials feel they are

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169/ U.S.C., Title 18, Chapter 47 (June 25, 1948, ch. 645, 62 Stat. 749).

over-regulated to the point of being stifled; FDA feels it lacks the authority necessary to enforce its regulations; and consumer groups claim the public is not adequately safeguarded against dangerous and ineffective drugs.

Bills which would amend the Food, Drug, and Cosmetic Act and attempt to correct the shortcomings in present law, have been introduced in successive congresses since the early 1960s, shortly after the passage of the Kefauver-Harris Amendments. These bills have either dealt with singular drug issues or comprehensive drug regulatory reform. Certain of the more recent bills are discussed below. They were selected because they have been repeatedly introduced over the years, they pertain specifically to drug testing, or they are currently receiving legislative attention.

Senator Gaylord Nelson has introduced a bill to establish a National Drug Testing and Evaluation Center in each Congress since the 91st. 170/ This bill would take the responsibility of testing out of the hands of the drug industry and place it with the Federal Government, with the drug manufacturers bearing the expense of the testing. The bill would establish the National Drug Testing and Evaluation Center as a part of FDA. A "drug testing review panel" would resolve disagreements and objections, and would be composed of three members -- one selected by the Secretary of DHEW, one chosen by the drug sponsor, and a third selected

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170/ Pending in the 96th Congress is Senator Nelson's bill, S. 774.

by the first two. The provisions of this bill would not preclude investigations carried out by drug sponsors, but results of such tests would be required to be made public; furthermore, any such tests involving human subjects would still require FDA authorization. Another interesting feature of the bill is the requirement that any new drug suitable for approval be significantly safer and more effective than any other drug, drugs, or combination of drugs already approved for marketing and used for the same purposes.

Congressman Steven Symms has sponsored bills since the 94th Congress which would remove the efficacy standard from the Food, Drug, and Cosmetic Act. 171/ Citing the present increases in approval time and the rising costs of drug development due to the efficacy requirement of the Kefauver-Harris Amendments, Mr. Symms feels the removal of the standard will alleviate the problem of delayed drug approval. Among other features, the bill would also reduce new drug application requirements and establish drug advisory committees in an effort to hasten drug approval.

In 1978, Congressman Tim Lee Carter introduced a bill on behalf of the American Medical Association. This bill would have allowed for the widespread distribution of a new drug prior to approval of its application. In addition, it would have shortened the time required for FDA to act on an application from 180 days to 120 days. 172/ This bill received no final action in the 95th Congress.

171/ Pending in 96th Congress is Rep. Symms' bill, H.R. 54.

172/ 95th Congress, H.R. 12485, by Rep. Tim Lee Carter.

Senator Richard Schweiker's 1979 bill would allow submission of a summary of investigations in lieu of full reports in the application for approval of a new drug. Further, this bill would require that any person intending to conduct a drug research investigation be registered to that effect. 173/

In 1978, a bill that Health, Education and Welfare Secretary Joseph Califano, Jr. described as "the first complete overhaul of the basic Federal law regulating drugs since 1938 . . . and the first major change since 1962," was introduced to the 95th Congress. Extensive hearings were held in both the House and the Senate, but the 95th Congress adjourned with no final action taken on the proposal. Early in the 96th Congress, the bill was re-introduced on behalf of the Carter Admininstration, with minor changes. Three days later, Senator Edward Kennedy and several cosponsors introduced their own version of the "Drug Regulation Reform Act of 1979," which included major modifications. Since it is the Kennedy bill which is currently receiving congressional attention, its provisions are discussed separately in the following section.

C. The "Drug Regulation Reform Act of 1979" [S. 1075]

1. Provisions of the Act. On introducing the Drug Regulation Reform Act of 1979, S. 1075, Senator Kennedy stated that:

173/ Pending in the 96th Congress is Senator Schweiker's bill, S. 1138.

> ...the drug investigation and approval process is too unpredictable during its investigational stage and too rigid during its approval stage. 174/

Briefly, the bill, as introduced on May 3, 1979, would do the following:

-- require that a summary of data from all drug tests be included in the New Drug Application [NDA];

-- require that test subjects to whom the drug will be administered will be under the direct supervision of the clinical investigator or persons responsible to the investigator;

-- require that, in ordinary test situations, test subjects be fully informed, and that voluntary consent be obtained in writing;

-- require that the health and rights of the test subjects be protected;

-- encourage investigators to obtain advice from FDA;

-- require FDA to issue written guidelines regarding protocols and methods for conducting drug investigations;

-- provide that a questionable drug may be administered to patients in extenuating circumstances where no other alternatives are available;

-- define "safe" as meaning the benefits outweigh the risks;

-- define "effective" as meaning that the drug will have the effect it is represented to have;

-- allow for the conditional approval of "breakthrough" drugs without waiting for completion of all clinical investigations;

-- define "substantial evidence" to include animal and clinical tests conducted by qualified persons;

174/ Kennedy, Edward. Drug Regulation Reform Act of 1979. Remarks in the Senate. Congressional Record, May 3, 1979: S5304.

-- allow for conditions to be imposed on approved drugs (limited distribution and dispensing, post-approval surveillance of drug use and experience, further testing in view of adverse effects or questions of efficacy, and batch certification);

-- allow the Secretary to appoint advisory committees in evaluating drugs;

-- establish a National Center for Drug Science composed of a Divison of Policy and Research and a Division of Clinical Pharmacology and Clinical Pharmacology Training (may conduct and support investigative research, shall conduct drug science policy research, shall conduct ongoing review and analysis of drug use, may make grants to training centers); and

-- establish a National Advisory Board on Drug Science (would consult with, advise, and make recommendations to the Director of the Center).

Other major provisions of S. 1075 not relating specifically to drug testing and approval pertain to civil penalties; compliance with an official compendium; labeling; drug promotion and advertising; a Federal Drug Index; educational programs; resolution of disputes; drug exports; the establishment of FDA as an agency in DHEW; and increased FDA authority.

The Administration's bill, S. 1045, includes many of the provisions found in S. 1075, but in more detail. One of the major differences between the two bills is S. 1045's proposed establishment of an extensive drug monograph process for new drug approval.

2. Criticism of the Proposed Legislation. Much of the criticism leveled at recent legislative proposals is in response to the Administration's 1979 bill, which is essentially the same as last year's bill.

The medical profession's objections to the 1978 bill were expressed in an article by Dr. John D. Ballin, director of the American Medical Association's Department of Drugs. 175/ Concerning drug testing and approval, significant areas of concern to physicians included:

-- post-marketing surveillance systems, requiring physicians to report drug experiences;

-- restricted distribution by FDA of selected drugs;

-- requirements that physicians obtain written consent in practice settings;

-- additional delay in the drug approval process; and

-- possible reductions in research due to increased regulatory burdens.

Many of the provisions causing the above concerns have remained in S. 1075, but with some modification.

The pharmaceutical industry is undoubtedly the most vocal critic of the legislation. After the introduction of what Secretary Califano referred to as a "consensus bill" in 1978, several spokesmen for the drug industry spoke up against specific provisions. The desirability of de-regulating the early phases of clinical testing was expressed on several occasions. Early clinical testing is generally considered safe, and without regulatory burdens at this step, the development of drugs would be hastened considerably. In 1978, Gerald Laubach, President of Pfizer Inc. suggested that the monitoring of these early studies could be transferred to the research review committees where the studies

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175/ Ballin, John C. Legislation, Regulation, Drug Lag, and New Drugs. Journal of the American Medical Association, vol. 241, March 30, 1979: 1405-1406.

are being done, saving time and needless regulation by FDA. 176/ C. Joseph Stetler, President of PMA, echoed this suggestion in congressional testimony in May 1979. 177/ He objected to the fact that FDA would retain the broad authority to issue "investigational use" regulations, which he felt resulted in delays in research. Eliminating FDA control over early testing, and placing the monitoring of these studies with review committees, would solve this problem, he felt. 178/

The proposed establishment of a "third party" agency prompted skepticism which was expressed at a July 1978 conference to consider the 1978 bill. Participants questioned the fiscal support for such a center, but agreed that support for clinical pharmacology was a good idea. It was felt that the center would be assigned too many tasks, some of which were unrealistic. Also, it was doubted that good staff would be attracted to such a group. While questioning the broad language pertaining to the research functions of the Center, conference participants nevertheless were in favor of the increased training support offered by the Center. 179/ Mr. Stetler's testimony May 18, 1979 voiced PMA criticism of S. 1075's establishment of a National Center for Drug Science. He stated that the

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176/ Laubach, Gerald. Drug Reform Prescription: Consult Doctors, Patients. Chemical Week, vol. 123, November 29, 1978: 5.

177/ Stetler, C. Joseph. Drug Regulation Reform Act of 1979. Statement presented to Senate Committee on Labor and Human Resource, Subcommittee on Health and Scientific Environment: unpublished. May 18, 1979: 8.

178/ Testimony of C. Joseph Stetler, May 18, 1979: 8.

179/ The Center for the Study of Drug Development. Report of Washington Conference on the Drug Regulation Reform Act of 1978 (conference held in Washington, D.C. on July 11, 1978). November 1978. p. 14.

PMA endorses its creation, but not its potential to duplicate or initiate the kind of research assumed by industry.

Dr. Gilbert McMahon, past president of the American Society for Clinical Pharmacology and Therapeutics, testified at congressional hearings in June 1979. His criticisms and suggestions were based on his experience as a clinical investigator for 31 years. One of Dr. McMahon's major concerns was Phase 3 testing; he believed that if an effective post-marketing surveillance program was initiated, Phase 3 testing could be shortened considerably, thereby decreasing the number of studies and human subjects needed for them. 180/ Mr. Laubach expressed this sentiment earlier, in 1978, suggesting:

> ...[the] adoption of a policy that defines a program of post-marketing surveillance and continuing investigation of newly approved drugs, in lieu of overly long premarket testing. Guidelines for such studies should insure that pre-clinical investigations are appropriately curtailed or expedited to realize the social and economic aspects of surveillance. 181/

Mr. Stetler, on the other hand, in his 1979 testimony, objected to extensive post-approval monitoring of every drug, stating that it would be very costly and add little or nothing to patient safety. He felt that such surveillance should only be undertaken on the reasonable expectation that a drug is likely to be associated with serious adverse reactions. 182/

180/ McMahon, Gilbert. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology: unpublished. June 21, 1979: 4.

181/ Laubach, Gerald. Chemical Week, November 29, 1978: 5.

182/ Testimony of C. Joseph Stetler, May 18, 1979: p. 6.

Mr. Stetler's testimony represents PMA's views on S. 1075, as it was introduced on May 3, 1979. In general, PMA appeared supportive of the bill. Mr. Stetler had prefaced his statement with the following remarks:

> The new bill [S. 1075] embodies a much better approach to revising the Federal Food, Drug, and Cosmetic Act in that it seeks to amend existing law, rather than completely rewrite it. In our view, a totally new and untried legal mechanism would create more problems than solutions for both FDA and the industry...While more remains to be done if there is to be legislation which fully reflects the public interest and the legitimate concerns of health professionals and the regulated industry, we believe that S. 1075 can be modified to eliminate what we perceive to be its shortcomings. The bill encompasses a significant number of concepts which we believe would result in improvements to the drug laws. 183/

In addition to the objections already discussed (de-regulation of early clinical trials, the duties of a National Center, and the concept of post-approval surveillance), Mr. Stetler presented the following PMA criticisms of the bill: 184/

> -- too much abuse is possible with the FDA's authority to limit distribution and dispensing of questionable drugs--too many drugs could be restricted;
>
> -- PMA would like to see the authority to require post-approval studies more narrowly defined--also feels that marketing of such projects should continue while these tests are being conducted;

183/ Testimony of C. Joseph Stetler, May 18, 1979: p. 2.

184/ Ibid., pp. 3-11.

-- PMA opposes new definition of safety and efficacy, particularly the relative benefits and risks compared to other available therapies--this implies that the product should be better than its predecessors;

-- PMA objects to the retention of the 180-day approval period, and stresses that scientific decisions on drug approval receive input from the drug innovator, medicine, other sciences, and public representatives;

-- PMA objects to the omission of specific requirements to be met by second manufacturers of an already approved product--PMA feels these applicants should be required to submit in vivo [in humans] bioavailability and bioequivalence evidence; and lastly,

The above information is limited to those aspects of the legislation concerning drug testing, evaluation, and approval. To get a total picture of the industry's views on recent legislative proposals, it is necessary to examine the 1978 proposal, testimony presented to congressional subcommittees in 1978, the 1979 bill [S. 1075], the PMA critique of S. 1075 (185/), and testimony presented in recent 1979 hearings. 186/

On July 11, 1979, Mr. Fred Wegner, representing the American Association of Retired Persons and the National Retired Teachers Association,

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185/ Pharmaceutical Manufacturers Association. Analysis and Critique of S. 1075, 96th Congress: Drug Regulation Reform Act of 1979. May, 1979. 26 p.

186/ U.S. Congress. House. Committee on Science and Technology, Subcommittee on Science, Research, and Technology. FDA's Process for Approving New Drugs. Hearings, 96th Congress, 1st Session. Hearings held June 19, 21, and July 11, 1979, (unpublished).

U.S. Congress. Senate. Committee on Labor and Human Resources, Subcommittee on Health and Scientific Research. Drug Laws. Hearings, 96th Congress, 1st Session. Hearings held May 17 and 18, 1979, (unpublished).

submitted a statement to the House Science, Research, and Technology Subcommittee on behalf of older Americans. He said their major concern was that the health and safety of the American public be safeguarded and that FDA not yield to industry pressure to lower its standards for approving drugs. The provision in S. 1075 which would allow the conditional approval of "breakthrough" drugs prior to the completion of clinical tests was their biggest objection to the proposed legislation. Mr. Wegner said:

> This retreat in U.S. drug standards, if the breakthrough drug provision is enacted, poses a dangerous threat to the future health of American patients. It signifies the most pernicious fallout yet from the "drug lag" syndrome. 187/

187/ Wegner, Fred. FDA's Process for Approving New Drugs and General Accounting Office Study. Statement presented to House Committee on Science and Technology, Subcommittee on Science, Research, and Technology, (unpublished). July 11, 1979, p.8.

IX. CONCLUSIONS

The legislation being considered in the 96th Congress reflects issues raised in the 1968-1969 drug hearings. The potential for bias and the total control over drug testing by a profit-motivated drug industry may be countered with the "third party" concept. Institutional review committees, the development of a separate agency for drug testing and/or surveillance, and increased monitoring of drug trials may help insure the quality of the tests and the integrity of the data submitted for drug approval.

The issue of protecting human subjects in drug testing was discussed in the 1968-1969 hearings and gained increased attention in the 1970s. The establishment of review boards, increased regulations to protect the subjects, and increased surveillance should continue to be effective in reducing abuses of human test subjects.

Recent legislative efforts would elaborate the drug regulatory system, but, in so doing, may allow greater flexibility in the system. According to both FDA and drug industry officials, the broad terms of the present law restrict FDA's latitude in making decisions and prevent the agency from adopting alternative procedures in special situations.

One of the major goals of the pending legislation is to expedite the approval of promising new drugs. Critics have been outspoken in their

charges that present regulations have stifled drug innovation and have unreasonably increased the costs and time involved in drug development and approval. By expanding the authority of FDA in the post-approval period, the agency presumbly could afford to be a little less cautious in approving new drugs.

Current legislative proposals represent years of investigations, studies, reports, and recommendations involving the Congress, FDA, and the drug industry. The views of the public sector, the medical profession, Government agencies, and the pharmaceutical industry have been considered in developing these proposals. How Congress will choose to balance these competing interests remains to be seen.

53-690 O - 79 - 9

APPENDIX A: SELECTED BIBLIOGRAPHY

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APPENDIX B: TEXT OF THE NUREMBERG CODE*
(re: human experimentation)

1. The voluntary consent of the human subject is absolutely essential.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only be scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

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APPENDIX C

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor _____

Address _____

Date _____

Name of Investigational Drug _____

To the Secretary of Health, Education and Welfare
For the Commissioner of Food and Drugs
Bureau of Drugs (HFD-106)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, _____, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation: identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested

by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man--only animal and in vitro data are available--with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review committee. If the phases of clinical study as described under 10a and b above are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of instituional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that neither the sponsor nor the investigator has participated in selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations: that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of instituional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD-1571 will be regarded as providing the above necessary assurances. If the institution, however, has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same

procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD-1571. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, an additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 6.1 of this chapter.

Very truly yours,

SPONSOR	PER
	INDICATE AUTHORITY

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

STATEMENT OF INVESTIGATOR
(Clinical Pharmacology)

Form Approved
OMB No. 57-R0031

TO: SUPPLIER OF THE DRUG: *(Name and address, include ZIP Code)*

NAME OF INVESTIGATOR *(Print or Type)*

DATE

NAME OF DRUG

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical pharmacology with a new drug limited by Federal (or United States) law to investigational use.

1. A STATEMENT OF THE EDUCATION AND TRAINING THAT QUALIFIES ME FOR CLINICAL PHARMACOLOGY

2. THE NAME AND ADDRESS OF THE MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL PHARMACOLOGY WILL BE CONDUCTED

3. If the experimental project is to be conducted on institutionalized subjects or is conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that the investigator has not participated in the selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations; that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD-1572 will be regarded as providing the above necessary assurance; however, if the institution has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD-1572. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

FORM FD 1572 (1/76) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

4. THE ESTIMATED DURATION OF THE PROJECT AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED

5. A GENERAL OUTLINE OF THE PROJECT TO BE UNDERTAKEN *(Modification is permitted on the basis of experience gained without advance submission of amendments to the general outline, but with the approval of the review committee and upon notification of the sponsor.)*

6. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE GOVERN HIS RECEIPT AND USE OF THIS INVESTIGATIONAL DRUG

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigation that justifies clinical pharmacology.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects, and if the clinical pharmacology is suspended, terminated, discontinued, or completed, to return to the sponsor any unused supply of the drug. If the investigational drug is subject to the comprehensive Drug Abuse Prevention and Control Act of 1970, adequate precautions must be taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

c. The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.

d. The investigator is required to furnish his reports to the sponsor who is responsible for collecting and evaluating the results, and presenting progress reports to the Food and Drug Administration at appropriate intervals, not exceeding 1 year. Any adverse effect which may reasonably be regarded as caused by, or is probably caused by, the new-drug shall be reported to the sponsor promptly; and if the adverse effect is alarming it shall be reportec immediately. An adequate report of the clinical pharmacology should be furnished to the sponsor shortly after completion.

e. The investigator shall maintain the records of disposition of the drug and the case reports described above for a period of 2 years following the date the new-drug application is approved for the drug; or if no application is to be filed or is approved until 2 years after the investigation is discontinued and the Food and Drug Administration so notified. Upon the request of a scientifically trained and specifically authorized employee of the Department, at reasonable times, the investigator will made such records available for inspection and copying. The names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him,

_____

_____

_____

_____

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any patients or any persons used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

h. The investigator is required to assure the sponsor that for investigations involving institutionalized subjects the studies will not be initiated until the institutional review committee has reviewed and approved the study. (The organization and procedure requirements for such a committee should be explained to the investigator by the sponsor as set forth in Form FD-1571, division 10, unit c.)

Very truly yours,

Name of Investigator _____

Address _____

_____

APPENDIX D: MEMBERS OF THE REVIEW PANEL ON NEW DRUG REGULATION

REVIEW PANEL ON NEW DRUG REGULATION

NORMAN DORSEN, Chairman
Professor of Law
School of Law
New York University
New York, New York 10012

NORMAN WEINER, Vice Chairman
Professor and Chairman
Department of Pharmacology
University of Colorado Medical Center
Denver, Colorado 80260

ALLEN V. ASTIN
Director Emeritus
National Bureau of Standards
5008 Battery Lane
Bethesda, Maryland 20014

MARSHA N. COHEN
Assistant Professor of Law
Hastings College of the Law
San Francisco, California 94102

CHARLES E. CORNELIUS
Dean
College of Veterinary Medicine
University of Florida
Gainesville, Florida 32610

ROBERT W. HAMILTON
Professor of Law
School of Law
University of Texas
Austin, Texas 78705

DAVID P. RALL
Director
National Institute of Environmental Health Sciences
Post Office Box 12233
Research Triangle Park, North Carolina 27709

5/31/79

BUREAU OF DRUGS

SUMMARY DISTRIBUTION OF CHEMICAL TYPES WITHIN THERAPEUTIC POTENTIALS FOR ACTIVE INDs

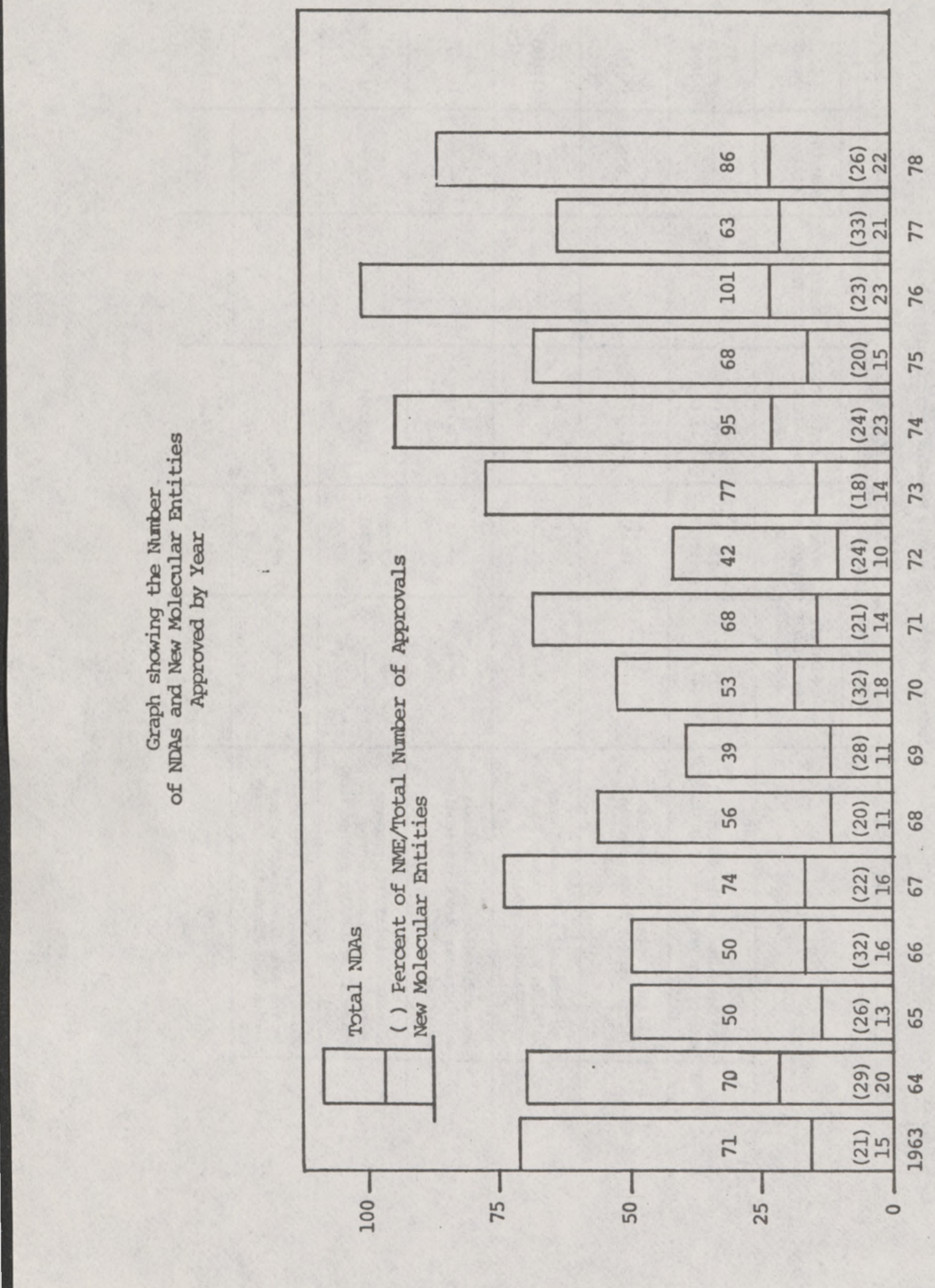
ALL DIVISIONS

		THERAPEUTIC POTENTIAL TYPE					
		A	B	C	D	E	
		IMPORTANT THERAPEUTIC GAIN	MODEST THERAPEUTIC GAIN	LITTLE or NO THERAPEUTIC GAIN	SPECIAL SITUATION	DESI/OTC CLAIM	TOTAL
1	New molecular entity (active moiety not yet marketed in U.S.)	20 (1.10%) 2.77%	82 (4.51%) 11.36%	609 (33.53%) 84.34%	10 (0.55%) 1.39%	1 (0.05%) 0.14%	722 (39.75%) 100%
2	New salt, ester or derivative (active moiety is marketed in U.S.)	——	6 (0.33%)	85 (4.68%)	——	——	91 (5.0%)
3	New formulation (compound marketed in U.S. but dosage form or formulation not)	2 (0.11%)	28 (1.54%)	218 (12.00%)	——	2 (0.11%)	250 (13.76%)
4	New combination (contains two or more components not previously marketed together)	2 (0.11%)	12 (0.66%)	59 (3.24%)	——	——	73 (4.01%)
5	Already marketed drug product (product duplicates a drug marketed in U.S. by another firm)	2 (0.11%)	7 (0.38%)	330 (18.17%)	2 (0.11%)	3 (0.16%)	344 (18.94%)
6	Already marketed drug product by the same firm (used for new indications for marketed drugs)	13 (0.71%)	22 (1.21%)	288 (15.85%)	3 (0.16%)	10 (0.55%)	336 (18.50%)
	TOTAL	39 (2.14%)	157 (8.64%)	1,589 (87.50%)	15 (0.82%)	16 (0.88%	1,816 (100.00%)

NDAs Approved during the Period, January 1, 1978 through December 31, 1978
Table shows Distribution of Approved NDAs Based on Drug Classification

		THERAPEUTIC POTENTIAL TYPE					
		A	B	C	D	E	
		IMPORTANT THERAPEUTIC GAIN	MODEST THERAPEUTIC GAIN	LITTLE or NO THERAPEUTIC GAIN	SPECIAL SITUATION	DESI/OTC CLAIM	TOTAL
1	New molecular entity (active moiety not yet marketed in U.S.)	5 (5.8%) 21.7%	9 (10.5%) 39.1%	9 (10.5%) 39.1%	—	—	23 (26.7%) 100%
2	New salt, ester or derivative (active moiety is marketed in U.S.)	—	1 (1.2%)	3 (3.5%)	—	—	4 (4.7%)
3	New formulation (compound marketed in U.S. but dosage form or formulation not)	1 (1.2%)	1 (1.2%)	15 (17.4%)	—	—	17 (19.8%)
4	New combination (contains two or more components not previously marketed together)	—	—	1 (1.2%)	—	—	1 (1.2%)
5	Already marketed drug product (product duplicates a drug marketed in U.S. by another firm)	—	2 (2.3%)	39 (45.3%)	—	—	41 (47.7%)
6	Already marketed drug product by the same firm (used for new indications for marketed drugs)	—	—	—	—	—	—
	TOTAL	6 (7.0%)	13 (15.1%)	67 (77.9%)	—	—	86 (100.0%)

APPENDIX G


Graph showing the Number
of NDAs and New Molecular Entities
Approved by Year
Total NDAs
( ) Percent of NME/Total Number of Approvals
New Molecular Entities
100
75
50
25
0
1963 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78
71 (21) 15
70 (29) 20
50 (26) 13
50 (32) 16
74 (22) 16
56 (20) 11
39 (28) 11
53 (32) 18
68 (21) 14
42 (24) 10
77 (18) 14
95 (24) 23
68 (20) 15
101 (23) 23
63 (33) 21
86 (26) 22
Year

APPENDIX H

HEW (FDA) 77-3040

GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS

September 1977

Comments on the contents of this publication are invited and should be addressed to the following office:

Marion J. Finkel, M.D.
Associate Director for New Drug Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

53-690 O - 79 - 10

FDA BUREAU OF DRUGS CLINICAL GUIDELINES

(This list is incomplete. Additional Guidelines will be published in early 1978)

FDA 77-3040	General Considerations for the Clinical Evaluation of Drugs
FDA 77-3041	General Considerations for the Clinical Evaluation of Drugs in Infants and Children
FDA 77-3042	Guidelines for the Clinical Evaluation of Antidepressant Drugs
FDA 77-3043	Guidelines for the Clinical Evaluation of Antianxiety Drugs
FDA 77-3044	Guidelines for the Clinical Evaluation of Radiopharmaceutical Drugs
FDA 77-3045	Guidelines for the Clinical Evaluation of Anticonvulsant Drugs (Adults and Children)
FDA 77-3046	Guidelines for the Clinical Evaluation of Anti-Infective Drugs (Systemic) (Adult and Children)
FDA 78-3047	Guidelines for the Clinical Evaluation of Anti-Anginal Drugs
FDA 78-3048	Guidelines for the Clinical Evaluation of Anti-Arrhythmic Drugs
FDA 78-3049	Guidelines for the Clinical Evaluation of Antidiarrheal Drugs
FDA 78-3050	Guidelines for the Clinical Evaluation of Gastric Secretory Depressant (GSD) Drugs
FDA 78-3051	Guidelines for the Clinical Evaluation of Hypnotic Drugs
FDA 78-3052	Guidelines for the Clinical Evaluation of General Anesthetics
FDA 78-3053	Guidelines for the Clinical Evaluation of Local Anesthetics
FDA 78-3054	Guidelines for the Clinical Evaluation of Anti-Inflammatory Drugs (Adults and Children)
FDA 78-3055	Guidelines for the Clinical Evaluation of Psychoactive Drugs in Infants and Children

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

J. Richard Crout, M.D.
Director
Bureau of Drugs

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS

INTRODUCTION

The objective of clinical investigations is to assess whether a drug is of value in the treatment or prophylaxis of a disease or condition, its risks or undesirable effects, and the relative relationship of these assessments. Investigations of this nature must be conducted in such a way that the participating subjects, or patients, are exposed to the least possible risk consistent with the anticipated benefit.

These guidelines have been developed from experience with prior drugs. The guidelines will require modification with completely new entities, active in a way never before experienced, although it is anticipated that the general principles will remain valid. The guidelines must not be used to force new compounds into their mold else the fruit of original ideas may be lost. History is replete with discoveries that could not have been made if the investigation was constrained by established methods.

The investigator, the sponsor, and the regulatory agencies must recognize the need in drug evaluation for the exercise of sound scientific clinical judgement by the investigator, based on his experience in the field of study, together with the highest regard for the rights, safety, comfort and well-being of the test subject or patient. Obviously, any aspect of an individual study, the nature and frequency of laboratory tests, period of drug administration, interval between visits, etc., while generally outlined, must remain subject to modification in the best interest of the patient. Because the investigator is responsible for administration of the investigational drug, he also must have the ultimate responsibility for the welfare of the subject or the patient. Institutional review and informed consent will provide additional safeguards for the test subject. The principles concerning institutional review and informed consent are stated in the March 13, 1975 FEDERAL REGISTER, Technical Amendments concerning "Protection of Human Subjects" (45 CFR Part 46) and the following have been extracted for the purpose of this guideline.

A. Institutional Review

1. An institutional Review Board must be composed of no less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the institution. In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas.

2. No member of a Board shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the Board.

3. No Board shall consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with the institution, apart from their membership on the Board.

B. **Principles of Informed Consent**

1. A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

2. a description of any attendant discomforts and risks reasonably to be expected;

3. a description of any benefits reasonably to be expected;

4. a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

5. an offer to answer any inquiries concerning the procedures; and

6. an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

Prior to onset of studies, investigators must determine criteria which will be used to reach a decision to discontinue the test drug. These criteria may be altered during the studies as safety dictates. To help protect the safety of the subject or patient, the sponsor must assume the responsibility of initiating and maintaining proper follow-up of patients through the investigator. There is some risk associated with every investigational drug; despite guidelines, complete safety cannot be assured.

The guidelines are intended as overall guides to the clinical investigation of drugs and as such must be concerned primarily with generalities. The place for specifics is in the protocols of individual investigators in which details can be specified much more precisely in relationship to the preclinical and clinical data available on the compound at the time of the proposed investigation.

While there are obvious advantages to outlining the general sequence for phases of drug evaluations, the cardinal logic behind serially conducted studies is that the result of each prior study influences the plan of the following study. Frequently, natural landmarks are apparent for the review of data and modification of plans. The early clinical data should be reviewed and evaluated by the sponsor and the FDA as they become available so that the continuing and expanding evaluation of the compound can proceed expeditiously.

While it is both rational and desirable to design studies with a specific plan to obtain specific information, the generation of data justifying conclusions other than those originally anticipated is a very valuable result of clinical investigation, and the significance of the data is in no way reduced because it was not anticipated in the original design.

These guidelines are concerned with human studies. For evey set of clinical guidelines, it is assumed that adequate preclinical investigations have been conducted to indicate that the drug does indeed merit human trials and that animal pharmacology and toxicology appropriate for the proposed clinical trials have been accomplished. Some of the specific guidelines describe in vitro or animal pharmacologic tests which are particularly appropriate for the drug class under study. Animal findings relevant, or possibly relevant, to the safety and effectiveness of the drug should be considered in designing specific clinical protocols.

DESIGN AND ANALYSIS CONSIDERATIONS

1. Statistical expertise is helpful in the planning, design, execution and analysis of clinical investigations and clinical pharmacology in order to ensure the validity of estimates of safety and efficacy obtained from these studies.

2. It is the objective of clinical studies to draw inferences about drug responses in well defined target populations. Therefore, study protocols should specify the target population, how patients or volunteers are to be selected, their assignment to the treatment regimens, specific conditions under which the trial is to be conducted and the procedures used to obtain estimates of the important clinical parameters.

3. Good planning usually results in questions being asked which permit direct inferences. Since studies are frequently designed to answer more than one question, it is useful in the planning phase to consider listing of the questions to be answered in order of priority.

4. Certain principles are generally followed in the conduct of clinical trials. These are, to a large extent, stated in the May 8, 1970 Federal Register Statement concerning "adequate and well-controlled clinical investigations" (21 CFR 314.111). The principles are as follows:

The need:

a. To clearly state the objective(s) of the study.

b. To define the selection criteria (including diagnostic criteria and reasons for exclusion) and to show comparability of the population studied with the population likely to receive the medication (target population).

c. To document the method of randomization and the analysis performed to verify how well the randomization procedure worked.

d. To plan the suitable size of a clinical experiment. This will also depend upon appropriate decisions concerning the precision desired:

(1) the degree of response one wishes to detect,

(2) the desired assurance against a false positive finding, and

(3) the acceptable risk of failure to demonstrate the response when it is, in fact, present in the population.

e. To include, when appropriate, comparison group(s), usually simultaneous.

f. To perform studies blind whenever feasible, as a means of avoiding patient and physician response bias and selection bias.

g. To use objective methods of observation where possible and appropriate.

h. To rigorously define response variables (parameters), including description of methods of observation and quantification.

i. To maintain strict adherence to the protocol, if possible, or to document any modifications that may be necessary or desirable.

j. To specify limitations imposed upon the study by failure to comply with the written protocol (withdrawals, failure of randomization to produce similar groups, etc.) with some idea of the effect the limitation might have on the result.

5. A statement as to the rationale for a particular length of the study may be helpful. A clinical trial should be of sufficient length so that efficacy or the lack of it can be clearly demonstrated.

6. Any pooling of data across investigators or studies should be accompanied by specific summaries for each investigator or study and a statement as to the rationale for pooling the results.

7. The report of findings should include a description and documentation of the statistical methods used. This description of the methods used should be adequate to demonstrate their appropriateness.

SELECTION OF SUBJECTS

The propriety of any given study and the selection of the subjects for the study must be viewed in the total context of the study. This includes, among other considerations, the qualifications of the responsible investigator, the investigational facilities available to him, the proposed plan of investigation, the amount of information available on the compound, the patient population available to the investigator, and the availability of adequate peer review.

However, **drugs should be studied in all age groups, including the geriatric, for which they will have significant utility.** See Sections on "Women of Childbearing Potential" and "Evaluation in Children."

NUMBER OF PATIENTS

Some of the specific drug class guidelines suggest the number of patients which should be included in certain types of studies, based upon previous experience with these studies. These numbers must not be considered as absolute. The overriding consideration should be that the planned studies will provide the desired data while keeping to a minimum the number of subjects at risk. This often requires the contribution of the clinical biostatistician in sample size estimation.

RANDOMIZATION OF PATIENTS

Although randomization of patients among various treatment groups is generally satisfactory when one is treating the same disease, it is often preferable to stratify patients prior to grouping them. This will help to ensure appropriate analysis of results among subgroups that may be more or less responsive to the drug.

STUDY CONTROL

Some of the guidelines suggest that placebo groups should be included in the very earliest trials of the drug. This is desirable, but need not be interpreted as a strict requirement. The purpose of the earliest human trials of a new compound is gradually to build up the dose to a pharmacologic effect or side-effect level. This can often best be done on an open (non-blind) basis. The most important requirement for this phase of clinical trial is that the patient be under careful and continuous observation. In some instances, initial efficacy evaluation can also be accomplished with least risk by open studies against a historic baseline. The speed with which blind comparisons with placebo and/or positive controls can be fruitfully undertaken varies with the nature of the compound.

During all phases of clinical investigation the objective in using a placebo is to control the study adequately. It should be recognized that there are other methods of adequately controlling studies. In some studies, and in some diseases, the use of an active control drug rather than a placebo is desirable, primarily for ethical reasons. If a drug gives a positive dose response, this in itself may constitute adequate control in some studies. In some diseases or conditions where the natural course of the disease or the condition is predictable and in which objective measurements of therapeutic or prophylactic response can be made, carefully executed open studies may be compared to the historical data to provide acceptable evidence

of efficacy. Some studies should be designed to ascertain the degree of safety and effectiveness of the investigational drug in comparison with one or more marketed drugs for the same indication.

With the majority of investigational drugs, placebo and/or active drug controlled studies are necessary.

PATIENT COMPLIANCE

A serious problem in clinical drug evaluation is the degree of adherence by the patient to the dosage schedule. Protocols for controlled studies should state clearly how compliance is to be monitored and the degree of compliance acceptable for continuation in the study. If it is apparent at follow-up visits that patients are not complying, the reasons for their noncompliance should be determined. Efforts to keep these patients in the study should be as conscientious as those for the patients who are complying. All patients initially included in studies must be reported regardless of the degree of compliance. Inclusion of data on patient compliance and noncompliance enhances the credibility of a study. Certain aspects of noncompliance may necessitate evaluation within special subgroups, e.g., failure to take the drug under study, excessive use of alcohol, or use of other medications.

DOSAGE CONSIDERATIONS

It is desirable to ascertain a range of effectiveness so that the lowest effective dose and, when feasible, the highest safe and effective dose are determined.

Consideration should be given to varying dosage according to patient response in some double-blind placebo-controlled studies involving drugs where individual patient response is expected to be quite variable.

DRUG DYNAMICS STUDIES

Metabolic studies have on occasion led to the discovery of new drugs with a variety of therapeutic uses. Present knowledge of metabolic pathways may give clues to the chemist as to what metabolites will be formed.

In view of the well-established variations in metabolism among animal species, each drug must be evaluated individually regarding how much of the metabolic assessment is meaningful at each stage of the investigation. Uniform requirements for metabolic studies are therefore not appropriate.

The one standard requirement should be an attempt, at or soon after initial introduction into humans, to assess absorption characteristics (with exception of i.v. preparations) and plasma half-life by chemical determination of blood, urine, and fecal levels after single and multiple doses. Metabolic studies in humans may confirm whether man's metabolic disposition of the compound is similar to one or more of the animal species used in the preclinical pharmacology, toxicology and metabolic studies.

A search for drug metabolites is frequently incorporated in the study of a new drug, but at this time, with certain exceptions, not enough is understood about the relevance of these findings to assessment of safety and effectiveness. Animal studies, however, will often allow a judgement about whether drug action or toxicity involves a metabolite. A complete study of drug metabolism should be contingent upon the specific drug in question, its potential usefulness and stage of development.

Generally, early detailed metabolic studies in humans are not warranted. The technical problems involved may be great enough to preclude such studies altogether. Where feasible,

however, they should be performed along with the clinical studies since they may be of assistance in the design of the later clinical trials.

In the later stages of clinical trial, since the drug is administered to large numbers of patients, more detailed investigations on metabolism and protein binding are indicated.

Controlled studies for drug interactions and enzyme induction are highly desirable during the course of the clinical trials. Drugs which are frequently administered concomitantly should be studied in patients with the disease under treatment by the investigational drug. Obviously, from the practical standpoint, a selection must ordinarily be made. For example, a patient with arteriosclerotic heart disease and angina pectoris, receiving an investigational coronary vasodilator, may be on concomitant diuretic, anti-hypertensive, sedative, or hypoglycemic drugs. Drugs from these categories should be chosen. A patient on a gastric secretory depressant investigational drug for peptic ulcer might also be expected to be on a sedative and/or antacid concomitantly. Whichever drugs are chosen for the study of drug interactions, the information developed should ultimately be placed in the package insert.

TESTS FOR SAFETY

Both the nature and frequency of laboratory and other tests necessary for safe clinical evaluation vary with the compound. At times a clinical observation can be an earlier and more dependable index of an effect than a laboratory test with which that effect correlates. While specific laboratory tests are listed in some of the guidelines, it should be remembered that the most desirable tests to be used change with evolvement of new technology.

DEFINITIONS AND GUIDANCE

DEFINITIONS

Phase I, Clinical Pharmacology is intended to include the initial introduction of a drug into man. It may be in the usual "normal" volunteer subjects to determine levels of toxicity, and, when appropriate, pharmacologic effect, and be followed by early dose-ranging studies in patients for safety and in some cases early evidence of effectiveness.

Alternatively, with some new drugs, for ethical or scientific considerations, the initial introduction into man is more properly done in selected patients. **When normal volunteers are the initial recipients of a drug, the very early trials in patients which follow are also considered part of Phase I.**

The number of subjects and patients in Phase I will, of course, vary with the drug but may generally be stated to be in the range of 20-80 on drug.

Drug dynamic and metabolic studies, in whichever stage of investigation they are performed, are considered to be Phase I clinical pharmacologic studies. While some, such as absorption studies, are performed in the early stages, others, such as efforts to identify metabolites, may not be performed until later in the investigations.

Phase II, Clinical Investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on closely monitored patients of limited number. Seldom will this phase go beyond 100-200 patients on drug.

Phase III, Clinical Trials are the expanded controlled and uncontrolled trials. These are performed after effectiveness has been basically established, at least to a certain degree, and are intended to gather additional evidence of effectiveness for specific indications, and more precise definition of drug-related adverse effects.

Phase IV, Postmarketing Clinical Trials are of several types:

1. Additional studies to elucidate the incidence of adverse reactions, to explore a specific pharmacologic effect, or to obtain more information of a circumscribed nature.

2. Large scale, long-term studies to determine the effect of a drug on morbidity and mortality.

3. Additional clinical trials similar to those in Phase III, to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data which would ordinarily be obtained before marketing.

4. Clinical trials in a patient population not adequately studied in the premarketing phase, e.g., children.

5. Clinical trials for an indication for which it is presumed that the drug, once available, will be used.

PHASE I STUDIES

A. Subject and Setting

The studies should ordinarily be performed in adults who are hospitalized or are in other settings permitting close observation. Females who are pregnant, or are at risk of becoming pregnant, should be excluded.

In most cases, "normal" volunteers are involved in the initial studies, except when their use is contraindicated because of the potentially toxic or pharmacologic nature of the drug. With respect to the use of "normal" subjects it should be recognized that few people are literally normal in all respects. This term should be interpreted with caution and should mean volunteers who are free from abnormalities which would complicate the interpretation of the experiment or which might increase the sensitivity of the subject to the toxic potential of the drug. Individuals with mild, but stable, illnesses may be considered for inclusion in the initial study of a drug, e.g., patients with mild, uncomplicated hypertension or arthritis. It is permissible, even desirable, to include subjects with certain abnormalities for which the drug is indicated, e.g., otherwise healthy subjects with hyperlipoproteinemia if an antilipemic agent is being studied.

In lieu of, or supplemental to, the use of "normal" volunteers, in some or many cases, it may be feasible (and in some cases desirable or mandatory) to utilize patients with the disease to be treated. Several small, closely-followed studies may be performed in a metabolic ward or other institutionalized situation. In most cases, women of childbearing potential, children, and patients with serious primary disease and serious unrelated problems (e.g., cardiac, hepatic, renal, hematologic abnormalities) should be excluded from Phase I. In general, patients receiving concomitant drug therapy should be excluded, except perhaps where the concomitant therapy is considered mandatory (e.g., malignancy) or routine (e.g., salicylates in rheumatoid arthritis). Even when concomitant therapy is considered routine, every effort should be made to design and execute trials excluding the concomitant therapy, provided this is consistent with ethical principles of patient care. In general, outpatients should not be utilized as initial recipients of an investigational drug. Exceptions may include but are not limited to:

1. A drug which has been extensively studied abroad.

2. Combinations of well-known drugs.

3. Drugs which have been studied previously for other indications.

4. Drugs whose pharmacologic activity is so well-known that it is considered safe to utilize outpatients, e.g., corticosteroids, estrogens.

5. Marketed drugs which are being investigated by other manufacturers.

6. New formulations of known drugs.

7. Topical preparations.

In cases 1, 3, 5, and 6 it is usually feasible to bypass Phase I and proceed directly to Phase II.

Hospital employees or adult students (volunteers) may, in some cases, be utilized as initial recipients of an investigational drug since they can be under the supervision of the clinical investigator by day, and, if an emergency situation should arise during nights or week-ends, they are knowledgeable with respect to contacting the investigator or other physician.

B. Qualifications of Investigators

Phase I studies involving "normal" volunteers should ordinarily be performed by investigators skilled in initial evaluation of a variety of compounds for safety and pharmacologic effect. Where patients with a specific disease are being studied, the investigators involved should be experts in the particular disease categories to be treated and/or in evaluation of drug effects on the disease process.

C. Procedures

Pretreatment physical examinations and the following laboratory tests should be performed to screen out individuals with medically significant abnormalities: CBC including platelet estimate, urinalysis, BUN (or serum creatinine), liver function studies, FBS (or 2 hour postprandial blood sugar), ECG and any other specifically indicated for the drug under study.

For individuals who will probably be involved in repeated drug testing, G-6-PD deficiency screen should be performed.

Prior to administration of a new drug, whenever feasible, all patients or subjects shall have been off previous drugs (including "over-the-counter" drugs) for at least two and preferably four weeks. In some cases where the previous drug has a prolonged duration of action, a longer "washout" period will be required for return to physiologic state.

1. Single Dose Studies

In a rising single dose study, no subjects should be placed upon the next higher dose until sufficient exposure has occurred with the immediately preceding dose to ascertain that serious adverse effects have not occurred.

The number of subjects in the prolonged dose study is optional. It is desirable to begin with a small group, e.g., 5 on drug and 5 on placebo for a period of 5-7 days to observe for adverse effects, and then move to larger groups. The inclusion of a placebo group is desirable because of the high incidence of side effects reported in institutionalized subjects involved in drug studies (sometimes as many as 40-50% of subjects on placebo report side effects) and because of the possibility of intercurrent infections which may produce laboratory abnormalities and symptoms which could be attributed erroneously to the drug.

In this connection, because of the occasional occurrence of infectious hepatitis outbreaks in an institutionalized setting with resultant hepatic function abnormalities which could be attributed to drug (if the placebo patients happen to be uninvolved

in the outbreak), it may be desirable to perform the prolonged dose study in two or more institutions. Despite the limitations of the test, it may be of interest to determine the presence of Hepatitis-Associated Antigen when one is uncertain about the etiology of hepatic function abnormalities occurring during drug testing.

The prolonged dose placebo-controlled study is usually performed double-blind. The subjects should be seen at least once daily, physical examinations should be performed during and post-therapy and all laboratory examinations should be repeated at least once weekly. The duration of drug administration in the prolonged dose Phase I study, will, of course, vary with the nature of the drug. Where a drug is intended for chronic administration, a period of at least 4-6 weeks of continuous administration is usually utilized unless contraindicated by the toxicity or pharmacologic effect of the drug.

D. Additional Considerations

1. Recent experience with ECG's in supposedly normal adults has demonstrated the occurrence of T wave ST segment abnormalities, bundle branch block, arrhythmias, etc. In cases where these occurred only in the drug group, the sponsors and the FDA have had to conclude that the changes may have been drug related. Therefore, it is desirable to gather a significant amount of ECG data under standardized conditions in "normal" volunteers, monitored and interpreted by experts, to provide information on incidence of various ECG changes.

2. Specialized laboratory tests are indicated from the safety and pharmacologic standpoint when animal studies have demonstrated a potential problem in a target organ or when it is desirable to measure certain pharmacologic effects.

3. Special attention to the possible appearance of certain physical findings is indicated when previous experience with a class of drugs has revealed the occurrence of such abnormalities in animals or man.

4. Blood level studies should be performed with single and with multiple doses of the drug. Sometime during the clinical trials of Phase II and III, methods for determination of blood levels of drug using the non-tagged compound should be developed, if feasible; such delay in development of these methods should be considered only when it is likely that their development would be too difficult and time-consuming to be worth the effort during Phase I.

PHASES II AND III STUDIES

A. Subjects

Patients selected for early Phase II studies should ordinarily be free of hematologic, hepatic, renal, cardiac or other serious diseases. To avoid possible interference with assessment of safety and effectiveness of the investigational drug, they should be receiving no concomitant therapy, if feasible.

Patients in later Phase II studies and Phase III studies may be included (cautiously) if they have concomitant diseases and concomitant therapy since they would be expected to be representative of certain segments of the population who will be receiving the investigational drug following approval for marketing.

B. Qualifications of Investigators

Phase II studies should be performed by investigators who are considered experts in the particular disease categories to be treated and/or in evaluation of drug effects on the disease process. Phase III studies may be performed by experts and/or experienced clinicians, depending upon the nature of the studies.

C. Procedures and Additional Considerations

In Phase II, the frequency of the visits and of the laboratory tests will vary depending upon the nature of, and the safety of, the drug. For some drugs, daily supervision may be necessary. Patients should ordinarily be seen by the investigator at least weekly (or more frequently) for two or four weeks (the duration is dependent upon the number of and the results of Phase I studies and the chemical nature of the drug). Specialized "safety" and pharmacologic laboratory tests should be performed as required by the nature of the drug. Ordinarily, visits should then be biweekly for another six to eight weeks. After three months patients may be seen at monthly intervals for two or three months and bimonthly thereafter. Routine "safety" laboratory tests should be performed at frequent intervals. (CBC's should include platelet estimates.)

When the investigational drug or another active compound is altered significantly in manufacture or use of excipients in order to accomodate a single or double-blind trial, blood level studies (or urinary excretion studies, if blood level studies are not feasible) should be performed to indicate that the alteration has not materially affected its absorption or excretory process. Merely placing a crushed tablet in a gelatin capsule as a means of blinding, for example, would not require bioavailability studies, if dissolution rates are not affected. Any significant change in formulation or manufacture of the investigational drug during the course of late Phase II or Phase III clinical trials will require bioavailability studies so that meaningful comparison can be made among the clinical trials performed with the various formulations.

For chronically administered drugs which are known to be absorbed, complete ophthalmologic examinations (pre- and post-drug) should be performed in a representative number of patients followed for six months, or, preferably longer, on drug. For drugs that are administered for shorter periods in clinical trials, eye examinations should be performed at the end of drug administration; however, the possibility of delayed effects on the eye should be considered.

WOMEN OF CHILDBEARING POTENTIAL

A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomized or whose husbands have received or are utilizing mechanical contraceptive devices. Women in certain institutions, e.g., prisions, although of childbearing potential, could be considered as not in the appropriate environment to become pregnant during administration of an investigational drug. However, women in mental institutions could become pregnant.

In general, women of childbearing potential should be excluded from the earliest dose ranging studies. If adequate information on efficacy and relative safety has been amassed during Phase II, women of childbearing potential may be included in further studies provided Segment II and the female part of Segment I of the FDA Animal Reproduction Guidelines have been completed. All three Segments should be completed before large-scale clinical trials are initiated in women of childbearing potential.

In some cases, women of childbearing potential may receive investigational drugs in the absence of adequate reproduction studies in animals. These include, for example, the use of the drug as a life-saving or life-prolonging measure; use of a drug belonging to a class of compounds (e.g., anti-metabolites) where a teratogenic potential has already been established in animals; use of women who have been institutionalized for a time period adequate to establish a non-pregnant state.

When an investigational drug is used in a woman of childbearing potential for treatment of a serious disease and animal reproduction studies have not been performed, the lack of reproduction studies should be pointed out and fully informed consent should be obtained.

Pregnancy tests should be performed prior to introduction of the investigational drugs and the patient should be advised about suitable contraceptive measures.

For drugs that are absorbed systemically, transplacental passage and secretion in milk of the drug should be assumed until proven otherwise. Fetal follow-up should be carried out in women who become pregnant while on the drug. Excretion of the drug or its metabolites in the milk of lactating women should be determined, when feasible, prior to use of the drug in nursing mothers.

MALE REPRODUCTIVE SYSTEM

Where testicular abnormalities or abnormalities of spermatogenesis have occurred in experimental animals or where chromosomal abnormalities are anticipated (e.g., alkylating agents), the criteria for inclusion of males in Phases I, II and III depend upon the nature of the abnormalities, the dosage at which they occurred, the disease being treated, the importance of the drug, and the duration of drug administration. In some cases, special written consent forms, even in Phase III, may be required.

EVALUATION IN CHILDREN

Drugs with a significant potential for use in children and neonates should be evaluated in these age groups. Usually, studies in children are not attempted until there has been considerable experience in adults (i.e., late Phase II or early Phase III in adults). With certain drugs, of course, early use in children is warranted.

When studies are performed in children, it is preferable to begin with older children, followed by younger children, infants and prematures.

Detailed comment on pediatric studies is contained in the Guideline entitled "General Considerations for the Clinical Evaluation of Drugs in Infants and Children."