Y4
Sci 2
96/HHH

A11207 504658

1925-A

DOCUMENTS

GOVERNMENT
Storage

JAN 21 1981

FARRELL LIBRARY
KANSAS STATE UNIVERSITY

[COMMITTEE PRINT]

THE FOOD AND DRUG ADMINISTRATION'S PROCESS FOR APPROVING NEW DRUGS

REPORT

PREPARED BY THE

SUBCOMMITTEE ON
SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

COMMITTEE ON
SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

NINETY-SIXTH CONGRESS

SECOND SESSION

Serial HHH

NOVEMBER 1980

Printed for the use of the Committee on Science and Technology

---

U.S. GOVERNMENT PRINTING OFFICE

66-808 O WASHINGTON : 1980

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402

AUTHENTICATED
U.S. GOVERNMENT
INFORMATION
GPO

COMMITTEE ON SCIENCE AND TECHNOLOGY

DON FUQUA, Florida, *Chairman*

ROBERT A. ROE, New Jersey
MIKE McCORMACK, Washington
GEORGE E. BROWN, JR., California
JAMES H. SCHEUER, New York
RICHARD L. OTTINGER, New York
TOM HARKIN, Iowa
JIM LLOYD, California
JEROME A. AMBRO, New York
MARILYN LLOYD BOUQUARD, Tennessee
JAMES J. BLANCHARD, Michigan
DOUG WALGREN, Pennsylvania
RONNIE G. FLIPPO, Alabama
DAN GLICKMAN, Kansas
ALBERT GORE, JR., Tennessee
WES WATKINS, Oklahoma
ROBERT A. YOUNG, Missouri
RICHARD C. WHITE, Texas
HAROLD L. VOLKMER, Missouri
DONALD J. PEASE, Ohio
HOWARD WOLPE, Michigan
NICHOLAS MAVROULES, Massachusetts
BILL NELSON, Florida
BERYL ANTHONY, JR., Arkansas
STANLEY N. LUNDINE, New York
ALLEN E. ERTEL, Pennsylvania
KENT HANCE, Texas

JOHN W. WYDLER, New York
LARRY WINN, JR., Kansas
BARRY M. GOLDWATER, JR., California
HAMILTON FISH, JR., New York
MANUEL LUJAN, JR., New Mexico
HAROLD C. HOLLENBECK, New Jersey
ROBERT K. DORNAN, California
ROBERT S. WALKER, Pennsylvania
EDWIN B. FORSYTHE, New Jersey
KEN KRAMER, Colorado
WILLIAM CARNEY, New York
ROBERT W. DAVIS, Michigan
TOBY ROTH, Wisconsin
DONALD LAWRENCE RITTER, Pennsylvania
BILL ROYER, California

HAROLD P. HANSON, *Executive Director*
PHILIP B. YEAGER, *General Counsel*
REGINA A. DAVIS, *Administrator*
PAUL A. VANDER MYDE, *Minority Staff Director*

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

GEORGE E. BROWN, JR., *Chairman*

JAMES H. SCHEUER, New York
DONALD J. PEASE, Ohio
TOM HARKIN, Iowa
ALLEN E. ERTEL, Pennsylvania
KENT HANCE, Texas
WES WATKINS, Oklahoma

HAROLD C. HOLLENBECK, New Jersey
ROBERT W. DAVIS, Michigan
DONALD LAWRENCE RITTER, Pennsylvania

CONTENTS

	Page
Letter of transmittal and summary	v
Background	1
I. The Food and Drug Administration	1
(A) Purpose	1
(B) Legislative Background	3
II. Drug Research, Discovery and Development in the United States	13
(A) Preclinical Research (Discovery stage)	13
(B) Clinical Research (IND stage)	15
(C) Approval of New Drugs (NDA stage)	17
III. Recent Congressional Interest in Drugs	19
(A) The GAO investigation of FDA's new drug approval process	19
(B) Actions of Other Congressional Committees	20
(C) Science Research and Technology Subcommittee Hearings on the "FDA's Process for approving new drugs	23
Analysis of the Science, Research and Technology Subcommittee hearings:	
I. The U.S. Drug Lag	25
II. Health Impact of the Drug Lag	31
(A) Safety Benefits Do Not Justify Lag	31
(B) Need for Post Marketing Surveillance	34
(C) Therapeutic Losses for America's Sick	35
(1) Cardiovascular diseases	36
(2) Neurological diseases	42
(3) Respiratory diseases	44
(4) Gastrointestinal diseases	45
(5) Cancer treatment	46
(6) Drugs for other diseases	48
(D) The Need For a Variety of Drugs	51
III. Factors Contributing to the Drug Lag	53
(A) FDA Related Factors	53
(1) Slower FDA action to approve NDA's	53
(2) More cumbersome U.S. regulations for clinical testing	53
(3) FDA regulations and requirements may lengthen the preclinical research stage	54
(B) Sponsor Related Factors	55
(1) Economic potential of the drug	55
(a) Development costs vs profits	55
(b) Patent rights and licensing problems	55
(c) Lower costs of foreign clinical studies	56
(2) Technical problems	56
(3) Industry processing time	56
(4) Abandonment of one drug in favor of another	56
(5) Technology transfer of medical information	57
IV. Reasons for FDA's Slower Drug Approval Process	59
(A) Internal or management problems at FDA	59
(1) FDA communications with industry are slow	59
(2) Scientific and professional disagreements	59
(3) Management of human resources	61
(a) FDA reviewer changes during NDA review	61
(b) Uneven workload of reviewers	61
(c) Quality of personnel	61
(4) FDA could make better use of Information and Communication Systems	62
(5) Slow review process	62

IV. Reasons for FDA's Slower Drug Approval Process—Continued Page
(B) Problems with FDA's Regulations and Guidelines 62
(1) FDA regulations have become extensive and complex 63
(2) U.S. Clinical Studies 63
(C) International Differences 68
(1) Use of expert or advisory committees 68
(2) Public demand for openness 68
(3) Use of approved drugs 69
(4) Sponsor-agency relations 70
(5) Need for International Cooperation 71
V. Effect of the Drug Lag on Innovation and Productivity in the Pharmaceutical Industry 73
(A) More resources are being devoted to regulatory matters 73
(B) The number of NCE–INDs filed by U.S. firms is declining 74
(1) New Chemical Entities (NCEs) discovered by U.S. firms is decreasing 74
(2) IND filing is decreasing 75
(C) Other Drug Industry Innovation Disincentives 76
(1) Effective patent life for drugs is decreasing 76
(2) FDA reluctance to approve drugs of given types or for certain disease areas 76
(3) Drug export laws inhibit U.S. productivity 77
Conclusions 79
Recommendations 81
Appendixes:
A. Letter requesting GAO Study 83
B. Committee on Labor and Human Resources, United States Senate Summary of S. 1075 84

LETTER OF TRANSMITTAL AND SUMMARY

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, D.C., November 25, 1980.

Hon. DON FUQUA,
Chairman, Committee on Science and Technology,
U.S. House of Representatives,
Washington, D.C.

DEAR MR. CHAIRMAN: As you know, on June 19, 21 and July 11, 1979, the Science, Research and Technology Subcommittee of the Science and Technology Committee held a series of oversight hearings on "The FDA's Process for Approving New Drugs." Those hearings were a continuation of an important effort in this area, begun by the Hon. James H. Scheuer, former chairman of the Subcommittee on Domestic and International Scientific Planning Analysis and Cooperation. The speed with which Food and Drug Administration approves new drugs for marketing in the U.S. today has become a frequent target of criticism not only by drug manufacturers seeking to market the drugs but also by physicians wanting to use drugs which they know have been available in other technically advanced countries for months to years. Consumers are also concerned about this process with patients generally wanting the early benefits of new therapeutic advances, but some consumers are more concerned about being protected against possible unforseen side effects of drugs.

I am pleased to submit to you this document based on the Subcommittee's oversight hearings and on the considerable effort of the General Accounting Office.

In general, the Subcommittee hearings confirmed earlier impressions that there is, for certain categories of drugs, a "drug lag" within the United States as compared with some other technically advantaged countries. Examples of major, but not exclusive, factors for delays encountered in the availability of therapeutically important new chemical entities revolve about FDA's drug approval process and include: (1) internal management problems within the FDA, (2) complexity and extensiveness of FDA's guidelines and regulations, and (3) adversarial relationships between FDA and the pharmaceutical industry. The cumulative effect of these and other factors have resulted in well-documented drug availability delays. This has had an impact not only upon the overall wellness of the United States population but also upon the ability and willingness of drug manufacturers to invest in innovative approaches for the treatment of human diseases. A number of recommendations were made by hearing witnesses that would facilitate the FDA drug approval process while still insuring the safety of patients and the public and the efficacy of new prescription drugs introduced into the market place.

As a consequence of these findings, the Subcommittee intends to continue to exercise oversight on the scientific base and its application in FDA, the drug approval process and related guidelines and regulations.

With the cooperation in this endeavor of the FDA, other Congressional Committees, and outside experts, the Subcommittee believes that shortcomings in FDA's drug approval process can be remedied and the availability of therapeutic advances to the public can be maximized.

Sincerely,

GEORGE E. BROWN, Jr.,
Chairman, Subcommittee on Science,
Research and Technology.

BACKGROUND

I. THE FOOD AND DRUG ADMINISTRATION

A. Purpose

The Food and Drug Administration (FDA) is a scientific regulatory agency dedicated to achieve a single, overall objective: consumer protection. The FDA's mission is to insure that food is safe, pure, and wholesome; cosmetics are safe; human and animal drugs, biological products, and therapeutic devices are safe and effective; radiological products and use procedures do not result in unnecessary exposure to radiation; and all of these products are honestly labeled.

To carry out its mission the FDA is structured along product lines. Separate bureaus have responsibility for all regulatory activities, regarding specific classes of products, e.g., foods, drugs, veterinary products, radiological health products, biologics and medical devices (See the FDA organization, Figure 1)

In regard to drugs the agency is charged with the responsibility for insuring that drug products marketed in the United States are safe, effective, properly manufactured, and properly labeled for their intended uses. The agency discharges that responsibility by enforcing the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301). The act provides in section 505 (21 U.S.C. 355) that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has approved a new drug application (NDA) for it.

FDA approves an NDA only if the sponsor of the application first shows that the drug is safe and by substantial evidence that the drug is effective for the conditions prescribed, recommended, or suggested in the product's labeling that the sponsor submits to FDA and is properly manufactured. The statutory standard for substantial evidence is "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 . . . under the conditions of use . . . in the labeling or proposed labeling thereof." The NDA review and approval function is carried out by New Drug Evaluation section of the Bureau of Drugs.

The Bureau of Drugs regulates human prescription and over-the-counter drug products under applicable provisions of the Federal Food, Drug, and Cosmetic Act amended as discussed in Background section I.B. 3. In doing so the Bureau:

FOOD AND DRUG ADMINISTRATION

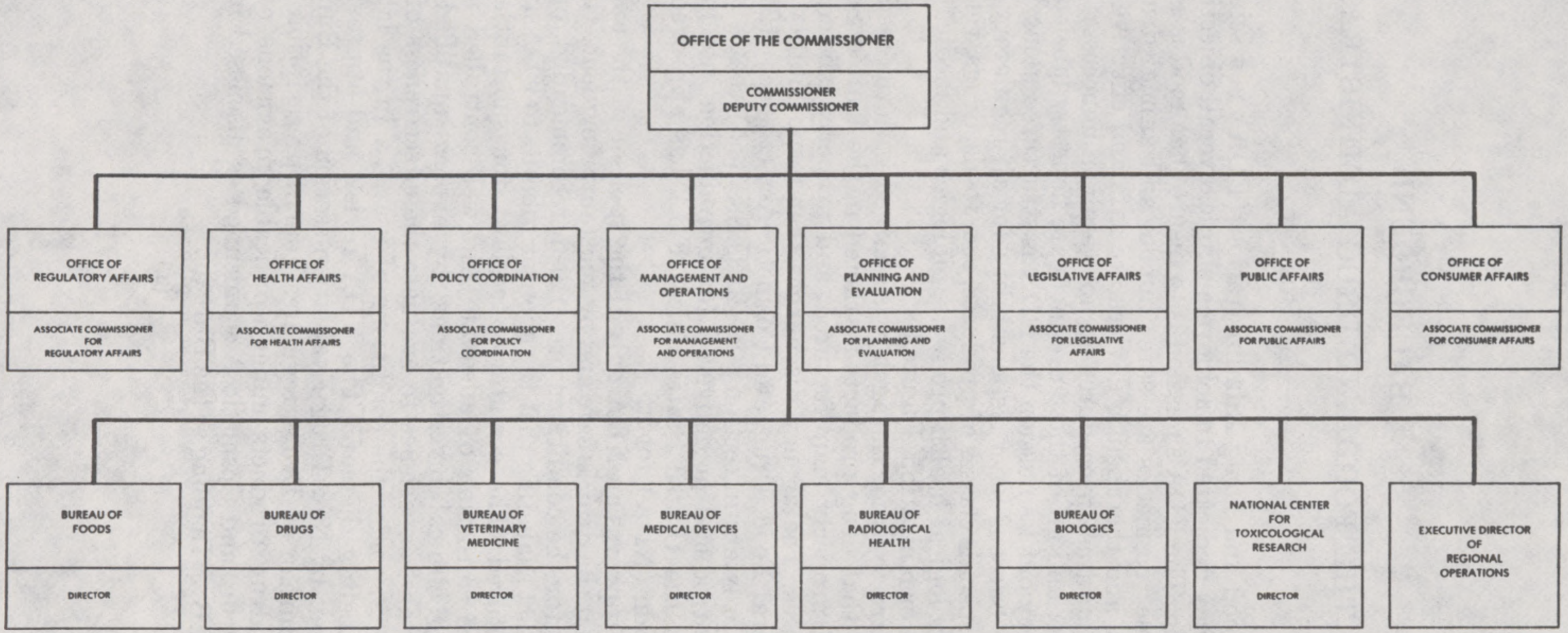

FIGURE 1

1. Evaluates evidence on the safety and efficacy of drugs before permitting them to be marketed; and establishes scientific standards which regulate their production and labeling.

2. Conducts research related to the composition, quality, safety, and efficacy of human drugs.

3. Establishes standards for the safety and effectiveness of over-the-counter drugs, and develops guidelines for the manufacture of human drugs.

4. Monitors the quality of marketed drugs through product testing, surveillance and compliance programs.

5. Collects and evaluates information on the manufacture, use, and adverse effects of marketed human drugs.

6. Monitors prescription advertisements and promotional labeling, and enforces requirements for accurate and balanced representations.

Certifies selected products prior to marketing.

Of these functions, the Science, Research and Technology Subcommittee is most concerned about the manner with which the agency and the Bureau of Drugs, in particular, carry out their purposes pertinent to the approval of pioneer new substances for marketing in the U.S.

B. Legislative Background*

Although the FDA can trace its beginnings to the Department of Agriculture in the year 1883, it did not become known as the Food and Drug Administration until 1930. At that time FDA's authority was based on the first Federal drug law.

The Food and Drug Act of 1906 [1] (the Wiley or Heyburn Act), which banned adulterated or misbranded food or drugs from interstate commerce and made it unlawful to manufacture such products; and the Sherley Amendment of 1912,[2] which prohibited false and fraudulent curative claims or therapeutic claims on a label.

By the early 1930's the inadequacies of the 1906 law and the Sherley Amendment were recognized as was the need for a comprehensive food and drug law.

In 1933, the Administration began drafting new legislation in an attempt to tighten the Federal regulation of food, drugs, and cosmetics. Its chief Congressional sponsor was Senator Royal S. Copeland. For five years the FDA bill, as modified by Senator Copeland, was debated and made little progress. Then, shortly after the "Elixir of sulfanilamide" disaster which resulted in over one hundred deaths, Congress adopted portions of the Copeland bill. The 1938 Food, Drug, and Cosmetic Act substantially revised the authority of the Federal Government to protect the public against adulterated and misbranded food and drug products.[3] In addition, cosmetics, which prior to this time were unregulated, were placed under Federal supervision.

---

*Much of the material in this part is excerpted from "A Brief Legislative History of the Federal Food, Drug, and Cosmetic Act," *Compilation of Selected Acts Within the Jurisdiction of the Committee on Interstate and Foreign Commerce,* House Committee on Interstate and Foreign Commerce. Committee Print 95–6. March 1977, p. 387.

[1] 34 Stat. 768, 59th Cong., 1st sess. ; June 30, 1906.

[2] 37 Stat. 416, 62d Cong., 2d sess. ; Aug. 23, 1912.

[3] 52 Stat. 1040, 75th Cong., 3d sess. ; June 25, 1938.

66-808 O - 80 - 2

Today the 1938 act and a series of amendments between 1941 and 1972 are the basis for the FDA's authority over drugs.

The Federal Food, Drug, and Cosmetic Act of 1938 (the Copeland Act)

The major drug provisions of the 1938 Act are outlined below:

1. Prohibited traffic in new drugs unless they had been adequately tested to show that they were safe for use under the conditions of use prescribed on their labels. Exemptions to these requirements were provided for drugs intended solely for investigational use by qualified scientific experts.
2. Required the labels of official drugs—those recognized in official compendia—to reveal any differences of strength, purity, or quality from the official standard (the 1906 act merely required that the label bear a true statement of the purity, quality, and strength of the product).
3. Required drugs intended for use in man to bear labels warning against habit formation, as in the case of narcotic or hypnotic drugs.
4. Required labeling of drugs to bear adequate directions for use and authorized exemptions only where protection of the public health was not involved.
5. Required labels to bear warnings against unsafe use, where drugs might be dangerous to health.
6. Required special precautionary labeling of drugs subject to deterioration.
7. Required official drugs to be packaged and labeled as prescribed by the official compendia.
8. Declared non-official drugs illegal if their standard of strength differed from the standard claimed.
9. Required the labels of non-official drugs to list the names of the active ingredients and to show the quantity or proportion of certain specified substances.
10. Deemed illegal any drug whose labeling was false or misleading in any particular.
11. Required any drug in package form to bear: (1) the name and place of business of the manufacturer, packer, or distributor, and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.
12. Prohibited traffic in drugs which might have been prepared or handled under unsanitary conditions.
13. Deemed illegal any drug whose container was made, formed, or filled so as to be misleading.
14. Forbade the use of uncertified and impure coal-tar colors in drugs.
15. Authorized factory inspection of establishments producing drugs, subject to certain conditions.
16. Authorized the procurement of transportation records and other documents necessary to establish Federal jurisdiction.
17. Provided increased penalties for violations.
18. Authorized the Federal courts to restrain violations by injunction.

The limitations imposed by the "false and fraudulent" provision of the Sherley Amendment were eliminated by prohibiting therapeutic claims that are "false or fraudulent".

With the exception of new drugs, the 1938 Act did not provide for automatic pre-market testing or approval. If the Federal government had reason to believe that a particular substance posed a hazard to the consuming public, it had to go to court to establish these hazards and the burden of proof of such fact rested with the Government.

In an effort to prevent another disaster such as the sulfanilamide poisonings, the Act did provide for pre-market clearance of new drugs to assure safety. Prior to marketing, manufacturers had to submit to the Food and Drug Administration full reports of investigations which had been undertaken to establish safety. Unless the FDA, within a specified period of time, issued an order finding that such safety had not been established, the manufacturer could proceed to market the drug. The FDA was also authorized to act beyond the initial stages of drug development and was permitted to remove from the market any new drug which it subsequently could prove unsafe.

It is important to note that the 1938 act did not require that a drug had to be proven effective, as well as safe, in order to be cleared for marketing. But in making its judgments about safety, the FDA did consider effectiveness. The relationship between safety and efficacy is considered elsewhere. It is only significant to note that the manufacturer of a product did not have to prove that his product did the things it was reputed to do.

Insulin and antibiotic certification amendments

In December 1941, Congress added a section to the 1938 Act requiring the Food and Drug Administration to batch-certify drugs composed, in whole or in part, of insulin before they could be placed on the market.[4] Each batch has to be tested for compliance with identity standards, and for the characteristics of strength, quality, and purity specified in official compendia. These tests were designed to assure safe and efficacious use of insulin products.

In 1943, the War Production Board requested the Food and Drug Administration to assay samples of each batch of penicillin then being produced for use by the armed forces. In 1945, shortly before penicillin was to be made available for use in the civilian sector, Congress amended the 1938 Act by adding a section calling for the batch certification of penicillin products.[5] This section of the Federal Food, Drug and Cosmetic Act has since been amended three times. In 1947, the batch certification requirements were extended to streptomycin.[6] In 1949, Congress amended the antibiotics section of the law (Sec. 507) to include chlorotetracycline, bacitracin, chloramphenicol, and their derivatives.[7] The Drug Amendments of 1962 extended the batch certification requirements to all antibiotics intended for use in man.[8]

Regulatory Amendments of 1948

In 1948, the Federal Food, Drug, and Cosmetic Act was amended to clarify the extent of the FDA's regulatory authority. The Act, based

---

[4] 55 Stat. 851, 77th Congress, 1st session ; Dec. 22, 1941.
[5] 59 Stat. 462, 79th Congress, 1st session ; July 6, 1945.
[6] 61 Stat. 11, 80th Congress, 1st session ; Mar. 10, 1947.
[7] 63 Stat. 409, 81st Congress, 1st session ; July 13, 1949.
[8] 76 Stat. 780, 87th Congress, 2d session ; Oct. 10, 1962.

on the commerce clause of the Constitution, was intended to exclude from interstate commerce articles that are misbranded or adulterated. However, a number of court decisions raised the question, "where did interstate commerce begin and where did it end?" Enforcement officials were of the opinion it went all the way from the producer in one state to the consumer in another.

In one of the cases raising this issue, the FDA instituted seizure of macaroni and spaghetti which had become contaminated while stored in a mining company warehouse. The goods were condemned and the claimant appealed. The court of appeals ruled that the food had ended its interstate journey when the adulteration occurred. The Supreme Court declined to review the decision.[9]

Congress was immediately asked to close this loophole in the law. The new legislation, also known as the Miller Amendment, after its principal sponsor, A. I. Miller, Representative from Nebraska, clearly gave the Government jurisdiction over products that became adulterated or misbranded after interstate shipment and at all levels of distribution, including retailing.[10]

The Durham-Humphrey Amendment of 1951

In 1951, the Congress passed another amendment of the Federal Food, Drug, and Cosmetic Act, popularly known as the Durham-Humphrey Amendment after the names of its sponsors.[11] The statute contains a legal definition of the kinds of drugs for human use which may be dispensed by the pharmacist only upon the prescription of a "practitioner licensed by law to administer such drugs." Thus it leaves to State medical practice laws and medical practice boards to determine who is qualified to prescribe drugs, just as State pharmacy laws and boards determine who is qualified to dispense drugs.

Under the amendment, it is unlawful to dispense a drug bearing the Rx Legend without a prescription or to refill a prescription for an Rx Legend drug without an authorization from the prescriber. The amendment is grounded in the principle that the physician should control the amount of medication given to his patients. A prescription or refill may be transmitted by telephone, but such authorizations must be promptly reduced to writing and be filed by the pharmacist. Certain narcotic drugs can only be dispensed upon written order of the practitioner. The law further required that prescription-restricted drugs be labeled with the Rx Legend, and that it is illegal to place this legend on drugs not so restricted. The fundamental purpose of the legislation was to provide the pharmacist with clear guidance as to which drugs may not be sold, or refilled, without a prescriber's authorization, as distinguished from those products which may be sold to the layman for self-medication (known as over-the-counter, or OTC drugs).

The Durham-Humphrey Amendment defined three categories of prescription drugs:

1. Hypnotic or habit-forming drugs that are specifically named in the law, and their derivatives, unless specifically exempted by regulation;

---

[9] *United States* v. *Phelps Dodge Mercantile Co.*, 157 F. 2d 453 (1946), cert. denied. 330 U.S. 818 (1947).

[10] 62 Stat. 582, 80th Congress, 2d session; June 24, 1948.

[11] 65 Stat. 643, 82d Congress, 1st session; Oct. 26, 1951.

2. A drug which is not safe for self-medication "because of its toxicity or other potentiality for harmful effect, or the method of use, or collateral measures necessary to its use";

3. A "new drug" which has not been shown safe for use in self-medication, and which, under the terms of an effective new-drug application, is limited to prescription dispensing.

Many drugs which are considered "safe," insofar as their inherent toxicity is concerned, must be restricted to prescription sale because of the conditions for which they are intended to be used, because of diagnostic techniques, or because of collateral therapeutic techniques which are required in connection with their use. In brief, the Rx Legend drugs are not safe enough for a layman to use in self-medication. The labels on such drugs do not, therefore, contain detailed directions for use, precautions, and so forth, which would be needed by the layman to use the drugs safely and effectively. The physician and the pharmacist, however, must be provided with such information and the Amendment requires that that manufacturer provide them with such data.

Drugs which are not restricted to prescription sale (over-the-counter-drugs) must bear adequate directions for safe and effective use and warnings against misuse which the layman needs to know. The distributor of OTC drugs is required by law to label the product with such information. Drugs which may legally be sold over-the-counter must bear a "7-point label:"

1. The name of the product.
2. The name and address of the manufacturer, packer, or distributor.
3. The net contents of the package.
4. The established name of all active ingredients and the quantity of certain other ingredients whether active or not.
5. The name of any habit-forming drug contained in the preparation.
6. Cautions and warning needed for the protection of the user.
7. Adequate directions for safe and effective use. Typical warnings tell how to use the medication safely—"Do not apply to broken skin;" when not to use the medication—"Do not drive or operate machinery;" and when to stop taking the drug.—"Discontinue use if rapid pulse, dizziness, or blurring of vision occurs." Other warning statements answer questions for the layman, such as whether he should see a physician—"If pain persists for more than 10 days or redness is present, or in conditions affecting children under 12 years of age, consult a physician immediately."

Factory Inspection Amendments of 1953

In 1952, the Supreme Court held that the 1938 Act did not clearly permit mandatory factory inspection.[12] One section of the act made it a criminal offense to refuse permission to inspect. However, another section provided that a factory could be inspected only with permission of the operator. The Court found these two sections to be "fatally inconsistent."

As a result of the Supreme Court ruling, Congress passed an amendment in 1953 to permit the FDA inspection, after written notice to the owner, without a warrant and without permission of the owner.[13]

---

[12] *United States* v. *Cardiff*, 344 U.S. 174.
[13] 67 Stat. 476, 83d Congress, 1st session; Aug. 7, 1953.

Although the mandatory inspection provision was passed, the legislative history developed during the floor debate on the bill made it clear that inspection should not include access to records other than shipping records and that inspectors should not be allowed to check formula cards, complaints files, personnel records, or prescription files.

Although the 1953 Amendment authorized factory inspection without a warrant, the Supreme Court held in 1967 that a business proprietor can refuse to admit a government inspector unless he has a search warrant. This decision led the FDA to issue guidelines for obtaining a warrant when an owner or manager refused to consent to inspection voluntarily.

The Drug Amendments of 1962 (the Kefauver-Harris amendments)

The Drug Amendments of 1962 were, like the 1938 Act, enacted into law following a serious drug incident, the "thalidomide disaster".[14] Use of thalidomide, a sedative, by pregnant women can cause a severe deformity of the child called phocomelia. Although the drug was never approved by the FDA for commercial marketing, it was distributed to doctors for experimental purposes. A 1962 survey by the FDA showed the drug was given to 3,897 women of child-bearing age, nine of whom gave birth to a malformed child.

Legislation to achieve many of the objectives of the 1962 Amendments, like the 1938 legislation, was pending before the Congress when the thalidomide incident occurred. Unlike the 1938 Act, however, the Drug Amendments of 1962 did not represent an entire revision of current law or the drafting of a completely new proposal. Instead, the legislation extended, expanded, and strengthened the regulatory authority of the Food and Drug Administration, particularly as to prescription drugs.

The changes brought about by the 1962 Amendments included the following:

1. The Food and Drug Administration was authorized to establish for drugs, by regulation, current good manufacturing practices. Drugs which are not manufactured under conforming methods or in conforming facilities are considered adulterated.

2. The factory inspection authority was widely expanded to all matters bearing on violations of the Act. Included within the reach of this authority are data concerning the qualifications of technical and professional personnel employed by the manufacturer. Each establishment must be inspected at least once every two years.

3. Every manufacturer had to register annually with the Department of Health, Education, and Welfare. This provision aids in identifying and inspecting all places where drugs are manufactured, and aids in certain enforcement areas. Drugs coming from non-registered plants are deemed misbranded.

4. The Amendments provided that a new drug cannot be marketed until the FDA approves it as having met the statutory requirements for safety and efficacy. The 1938 law permitted automatic clearance of drugs through lapse of time without FDA action. Approval was now conditioned upon the showing of "sub-

---

[14] 76 Stat. 870, 87th Congress, 2d session; Oct. 10, 1962.

stantial evidence" of efficacy, and the burden for proof rested with the manufacturer.

5. Labeling now took on a material bearing on the matter of new drug approval—it must not be false or misleading in any particular. This prohibition relates to the claimed effects of such drugs, as well as to other aspects of labeling.

6. The Secretary of HEW on finding an imminent hazard to the public health, could immediately suspend a new drug approval, with the manufacturer afforded an expedited hearing.

7. Withdrawal from the market of a previously approved drug could be made for any one of the following reasons:

(*a*) if its labeling is found to be false or misleading in any particular and it is not corrected within a reasonable time after notice from FDA;

(*b*) if, after reevaluation in the light of new evidence, its safety cannot be established or its claimed efficacy is not supported by substantial evidence;

(*c*) if, after reevaluation in the light of new evidence, it is found that manufacturing facilities, methods, or controls employed in manufacturing or packaging do not conform with standards of good manufacturing practices and are not changed after a reasonable period of time; and

(*d*) if the manufacturer fails to establish a system of maintaining adequate records, fails to make required reports, or refuses to give the FDA access to such records.

8. With respect to drugs already on the market, the manufacturer was now required to report promptly to the FDA information concerning adverse effects and other clinical experience or data relating in any way to safety and efficacy.

9. New authority was granted to prevent the testing of investigational new drugs, including antibiotics, on humans unless specified safety conditions are met, including submission of report of preclinical testing, including animal studies, and the obtaining of signed agreements from investigators that clinical work will only be done under personal supervision and experimental drugs will not be supplied to others.

10. Manufacturers who sought an exemption for investigational drugs had to secure from their scientific investigators assurance that they would obtain informed consent from the persons to whom the drugs are to be administered or from their legal representative (with certain exceptions).

11. Exemptions for experimental drugs from the new drug procedures were conditioned upon the keeping of records and the making of reports. This requirement would enable the FDA to evaluate the safety and efficacy of the drug in the event that a New Drug Application was filed at some later date.

12. All human antibiotics became subject to batch-testing and certification. This provision added 30 additional groups to the five previously subject to this procedure.

13. Changes were made in labeling requirements. The quantity of all active ingredients and specified inactive ingredients must be stated. Labels have to bear the established name of the drug designated under the name standardization authority provided for in the Act, or certain other official or common names where an established name has not been designated.

14. Prescription-drug advertising is required to show the established name (in half-size type similar to that for any other name used, such as a trade name), the quantitative formula to the same extent it is required on the label, and a true and non-misleading brief summary of adverse effects, contra-indications, efficacy, and other information for the guidance of physicians.

A much cited weakness in the 1938 law was the requirement that drugs had only to be shown safe before marketing; there were no requirements for the manufacturer to prove that his product was effective (efficacious) as well. However, in testimony before a Committee of Congress, FDA Commissioner George Larrick noted that the FDA, since 1938, had assessed the effectiveness of certain products when making safety-determinations in the case of drugs for use in life threatening or grave diseases: [15]

Basically we were saying that the dangerous characteristics of many drugs were such that they would automatically be outlawed unless they had some life-saving or other very beneficial aspects that outweighed these dangers.

Where the FDA could not establish that the product was safe, the manufacturer was free to proceed to market the product. In short, under the 1938 statute the manufacturer had the burden of proof that the product was safe, while the Government had the burden of proof to disprove efficacy. The 1962 Amendments now require the manufacturer to show both safety and efficacy.

Prior to 1962, the manufacturer was also under no obligation to report any information on adverse findings, after the product was introduced into the market, that would cast doubt on or disprove the safety of the product. The 1962 Amendment required the manufacturer to keep the FDA advised of adverse experience and other data which would shed light on the status of the manufacturer's product.

An important feature of the 1962 Act was the provision which enabled the Food and Drug Administration to require tests of efficacy for every product which was subject to the new drug provisions of the 1938 Act. In short, an efficacy review—which is still going on—could be made with respect to every new drug introduced between 1938 and 1963.

The Drug Listing Act of 1972

As of 1972, the Food and Drug Administration had no ready means of determining what drugs were actually being manufactured and commercially distributed by establishments registered under the Food, Drug, and Cosmetic Act except by periodic inspection of the establishments.

---

[15] Hearings on Drug Safety; House Intergovernmental Relations Subcommittee, pt. 1, pp. 185–86; Mar. 24, 1964.

In an effort to increase the FDA's regulatory tools in this area, legislation was introduced in the 92nd Congress to provide for a current listing of each drug manufactured, prepared, propagated, compounded, or processed by registrant under the Act. During the hearings on the proposed legislation, the Commissioner of the FDA stated that availability of a current inventory of drugs would substantially assist in the enforcement of Federal laws requiring that drugs be pure, safe, effective, and properly labeled. The legislation under consideration was passed and signed into public law on August 16, 1972.

66-808 O - 80 - 3

II. DRUG RESEARCH, DISCOVERY AND DEVELOPMENT IN THE UNITED STATES

In the U.S. the process from research to marketing approval for a new drug today, takes about 7 to 13 years and costs $30 million to $50 million. Both time and cost have increased dramatically in the last two decades.

The total process to discover, develop, test and gain marketing approval for a new chemical entity (NCE) can be divided into three major stages (refer to Figure 2 and above) :

	Years
1. Preclinical research aimed at the discovery and identification of a new drug which is sufficiently promising to study in humans	1–4
2. Clinical research to determine human efficacy and side effects (IND, Phases I, II, III)	4–6
3. FDA evaluation and approval of a new drug application (NDA)	2–3
Total	7–13

The total process is usually shorter for generic drugs and for drugs which are simply a new formulation of an already approved drug. This is due mainly to shortening of the preclinical and the clinical research stages. However, the time FDA takes to review and approve a New Drug Application (NDA) does not seem to vary greatly for new chemical entities when compared with NDA review and approval requirements for new formulations or generics. The GAO investigation, an important information resource for these hearings, is directed at the third stage of this process—the FDA's approval of new drug applications.

Many generic drugs, in cases where the pioneer drug was approved before 1962, are approved by an abbreviated new drug application process (ANDA). This process does not require as extensive phase I, II and III testing. For drugs approved prior to 1962, this approval process (ANDA) is carried out by the Division of Generic Drug Monographs, Bureau of Drugs. For drugs originally approved after 1962, various sections, depending on the product area, within the Division of New Drug Evaluation, Bureau of Drugs are responsible for ANDA. The ANDA is not the subject of the GAO investigation or of these hearings.

A. Preclinical Research Aimed at the Discovery of a Promising New Drug

Most preclinical research takes place in industry because of the multidisciplinary nature of drug research in the search for therapeutic break throughs and drug development which must be directed toward a common goal over a sustained period. With few exceptions, pharmaceutical industry research development and related decisionmaking activities involved in this process are not regulated directly by the FDA. FDA's requirements for NDA's do, however, affect the type and direction of research and other development activities which must be done

DISCOVERY, DEVELOPMENT AND APPROVAL

OF NEW DRUGS IN THE U.S.

Discovery research at pharmaceutical Companies

(1-4 years)

Company files IND with the FDA and if not denied, clinical research in humans begins
(4-6 years duration)

Company files NDA and awaits FDA approval before marketing new drug
(2-3 years)

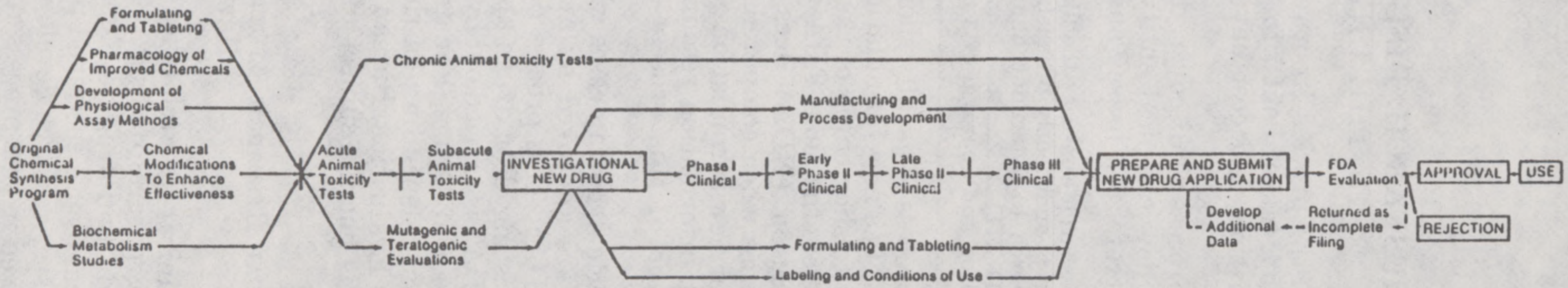

FIGURE 2

once a new chemical entity is identified. The research process begins with a pharmacotherapeutic concept. The scientist must have a biological mechanism to regulate and/or a chemical lead to follow, either of which must be important to the particular target disease. Because of the resources needed, the state of the knowledge of a disease area and the probability of scientific and/or marketing success are evaluated before the research process proceeds.

Once a chemical lead is established, interesting compounds are prepared by chemists and are examined in detail by pharmacologists with sophisticated techniques in a broad range of test systems, from subcellular particles to laboratory animals. The best compounds with potential therapeutic applications are then submitted to toxicological examination which usually includes determinations of lethal doses in at least three species of animals and pathological studies for detection of organ toxicity. An estimate is made of a therapeutic ratio by comparing a presumed effective dose in a series of animal models with toxic doses in the same species.

Potentially useful compounds are considered for clinical pharmacology. This is a crucial period in the life of a new chemical entity, and only a few compounds of hundreds synthesized will be investigated in man. Decisions on which of several analogs to proceed with is extremely difficult. Judgments must be made both with regard to the estimated therapeutic index and, after consideration of a number of other factors including duration of effect, oral absorption, and cost of production.

Compounds chosen for human study must then undergo additional toxicological evaluations and pharmacokinetic studies to determine how the drug is metabolized and excreted in animals. Finally, the drug must be prepared in a form which is stable and bioavailable. Preclinical research data on the chemistry, pharmacology, and toxicology of the promising compound selected for human studies is then submitted to the FDA in a document called a "Claimed Exemption for an Investigational New Drug" (IND).

B. Clinical Research—the IND Stage

The Food, Drug and Cosmetic Act states that research on a new drug in human beings can be done only after a notice of claimed exemption for an IND (investigational new drug) has been submitted to the FDA and at least thirty days have expired without notification from the FDA that studies may not commence. The prime purpose of the IND is to protect the safety of investigational subjects while developing the data on safety and effectiveness necessary to permit the marketing of the drug. A corollary responsibility of IND is to ensure the appropriateness and scientific design of studies under the IND so that the IND review process may efficiently anticipate and prevent problems which might arise in NDA review.

The considerations on which the FDA makes its decision to permit or restrict initial research include:

The protection of the human research subject.

The adequacy of animal studies already completed and analyzed.

The scientific merits of the research plan.

The qualifications of the investigator.

If the FDA does not reject the IND, and if Institutional Review Boards (IRBs) in the institutions in which the drug will be tested also approve, clinical studies in humans can begin according to three prescribed phases—Phase I, Phase II, and Phase III—as set forth in FDA regulations.

PHASE I

In this phase the clinical pharmacologist has the responsibility of administering the drug to a human volunteer for the first time. He must thoroughly review the preclinical data, and if more information is required additional pharmacological and toxicological investigations must be carried out.

After satisfactory completion of these studies, the drug is administered to a few volunteers, usually healthy subjects but also sometimes patients, in order to ascertain drug metabolism and excretion and also to estimate the potential of the drug for producing adverse effects. Drug administration begins at very low single doses and the dose is then increased very gradually. If single dose studies show no untoward effects, multiple dose studies will be initiated. Throughout all of these studies batteries of laboratory tests are also obtained. These investigations are concerned with detecting adverse effects and usually do not provide data concerning efficacy of the new drug in the disease state it is designed to treat. If adverse effects which would limit the use of the drug are found, the drug will be abondoned at this stage.

PHASE II

If there are no problems in human toleration of a drug the drug then enters phase II, and for the first time it is studied in patients with the disease which the drug is designed to treat. Relatively small numbers of patients are investigated intensively with specialized studies tailored to the type of drug and the disease to be treated. Again dosage protocols begin with single dose studies and then proceed to multiple dose studies. The objective is to determine whether the drug has the desired therapeutic effect, the dose range at which this effect occurs, and whether any adverse effects observed will limit the drug's usefulness. Lack of efficacy at this phase will result in drug abandonment. Drugs still considered to be effective and safe then enter phase III for more extensive clinical investigation.

PHASE III

In this phase hundreds and even thousands of patients are investigated. These studies take place in a clinical setting approximating the environment in which the drug will be used. Usually masked, comparative studies with placebo or a standard drug are carried out, and great care is taken to detect adverse reactions and potential interactions of the new drug with other medications. The clinical, pharmacological and toxicological data for a drug satisfactorily completing at least two adequate and well controlled phase III studies is then assembled in a New Drug Application and submitted for approval to the FDA's Bureau of Drugs. Only about one out of ten drugs for which an IND was filed will have sufficient merit to file an NDA.

C. Approval of New Drugs—the NDA Stage

The Federal Food, Drug and Cosmetic Act states that no new drug may be marketed in the United States unless an NDA (new drug application) has been approved for that drug by the FDA. To have an NDA approved, a manufacturer must submit substantial evidence showing the safety and effectiveness of the drug under the use proposed. Thus companies contemplating marketing of a new drug will generally have already done clinical trials to establish safety and effectiveness under one or more INDs as described above (Phase III).

The NDA must contain all information, both favorable and unfavorable, the sponsor has obtained through investigations relating to both the safety and the effectiveness of the new drug. It must also contain information on the process by which the drug is made and how the quality of the drug will be assured. Each NDA consists of about 2 to 15 volumes of summary material accompanied by about 10 to 100 volumes (occasionally up to 400 volumes 100,000 to 200,000 pages) of raw data.

By law, the FDA has one hundred and eighty days in which to review the NDA and either approve or disapprove the application. The FDA may withhold final action on the NDA pending the compilation and submission of additional data, if the applicant agrees to the extension. The grounds for refusing to approve an application are specified in the Act and regulations. Where the FDA proposes to refuse to approve the NDA, the applicant is notified of an opportunity for a hearing on the question of whether or not the NDA is approvable. In this review, FDA determines whether the drug is safe and effective, whether the drug can be manufactured consistently and whether the benefits of the drug when used properly outweigh the risks. The FDA must also approve the description of the drug (package insert) which will be distributed to the prescribing physician before a drug can be marketed.

The time the agency takes to approve new drugs has been steadily increasing. FDA review and approval of the paper work associated with NDA's took 14 months in 1963, but has doubled since then. The agency's own estimates of average times to approve an NDA are shown on the following table (Table 1). Coupled with the increasing time and costs required to approve NDA's, it needs to be recognized that this stage in the drug approval process represents a fraction of the increasing time and costs required for other stages in the process, for example, the clinical trial stage in Phase III of the IND process.

TABLE 1

Fiscal year	NDA's approved	Average elapsed time for NDA's (months)[1]
1971	62	37.3
1972	57	25.9
1973	52	27.5
1974	85	27.3
1975	71	22.3
1976	72	20.0
Transition quarter	15	25.8
1977	91	26.3
1978	80	33.3
1979	90	35.2

[1] Elapsed time from receipt of original NDA to final approval by FDA.

The following chart illustrates the pathway that an NDA takes through the FDA's process of review and approval (fig. 3).

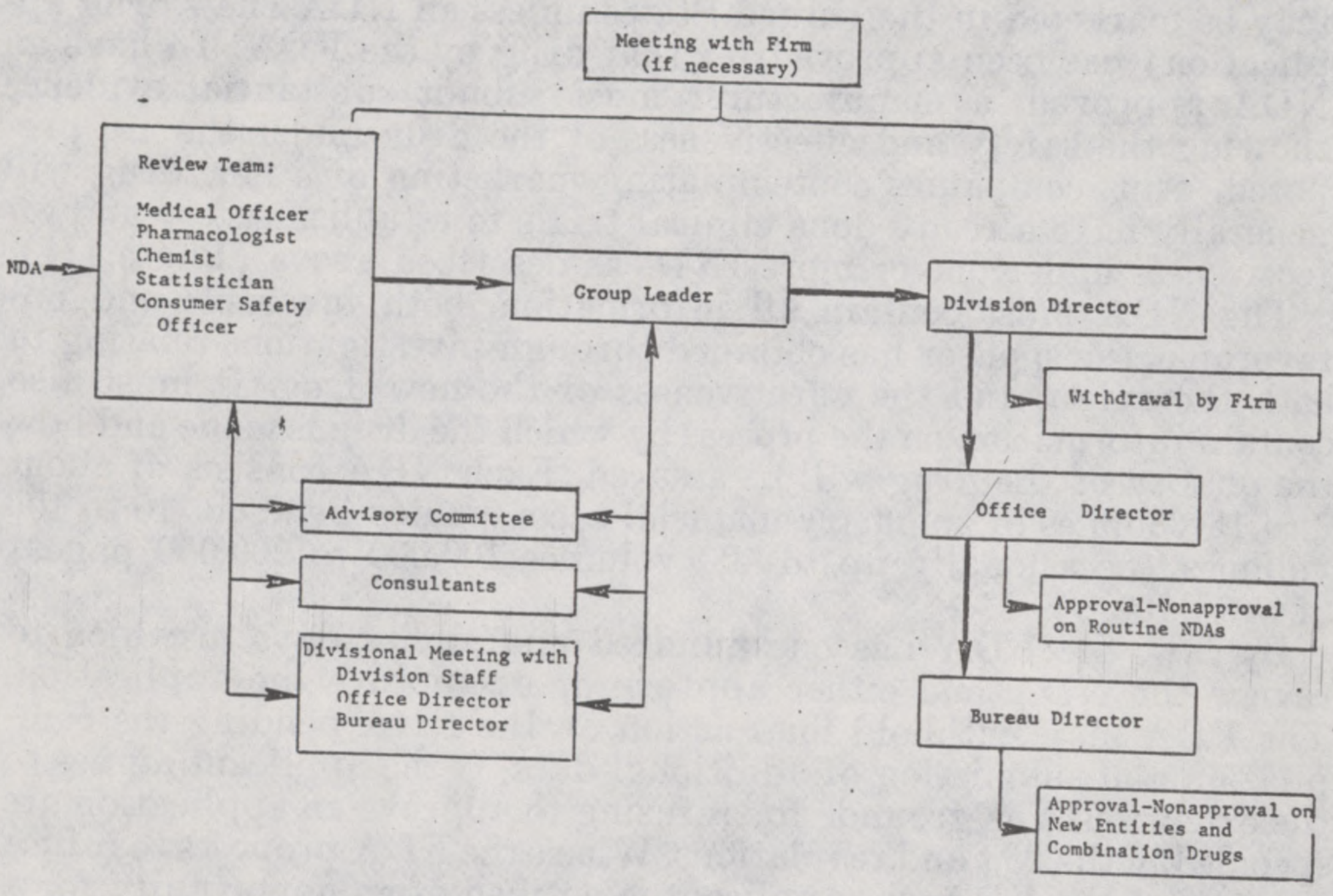

FIGURE 3.—FDA new drug application (NDA) review and approval process*

*From statement by Alexander M. Schmidt, M.D., Commissioner, Food and Drug Administration, PHS, DHEW, before the Subcommittee on Health, Committee on Labor and Public Welfare, United States Senate, Sept. 25, 1974.

III. RECENT CONGRESSIONAL INTERESTS IN DRUGS

A. The General Accounting Office Investigation of the Food and Drug Administration's New Drug Approval Process

The General Accounting Office (GAO) study was requested in May 1977, by Rep. James H. Scheuer, then chairman of Science and Technology's Domestic and International Scientific Planning, Analysis and Cooperation Subcommittee (see Appendix A). The study results from three basic questions raised by Mr. Scheuer in response to his concern about the "drug lag" and news accounts of demoralization plaguing personnel at FDA. These questions were:

1. Has there been an inordinate delay in processing and approving new drugs for marketing in the United States, and what improvements can be implemented to improve management and administration (including innovative computer technology)?

2. Have delays in drug approvals adversely affected the introduction in the United States of therapeutically important drugs that are available in other countries?

3. What improvements can be made in the FDA's risk-benefit analysis involving new drug approvals, and how does the agency's analysis compare with those of other technology developed countries?

Since that time the GAO has embarked upon a major two year study of procedures used by the FDA for new drug approvals. The study is claimed to have the wide support of the FDA, the pharmaceutical industry, and the medical research community. The GAO has divided its analysis into six major segments:

1. Analysis of the FDA's review process for approving 132 new drug applications (NDAs) filed in the calendar year 1975;
2. Results of interviews with FDA reviewers of new drug applications for their perceptions of the drug approval process;
3. Analysis of the workload of FDA physicians, chemists, and pharmacologists involved in the review of new drug applications;
4. Review of the FDA's use of scientific and management information systems in its drug approval activities;
5. Comparison of drug procedures in Canada and eight European countries with those in the United States; and
6. Views and concerns of the drug industry, pharmaceutical and medical associations, and other knowledgeable members of academia and FDA officials.

GAO testimony at the June 19, 1979, hearing was an initial public release of some information on this study.

The final GAO Report on this study dated May 28, 1980 is available from the General Accounting Office (HRD–80–64).

66-808 O - 80 - 4

Major conclusions reached by the May 28, 1980 GAO report are as follows:

1. FDA's approval process is lengthy, and it often takes almost as long to approve an important drug as to approve drugs of less importance.
2. The lengthy approval process delays the benefits important drugs can provide to the public.
3. GAO's analysis of the 132 new drug applications submitted in 1975 showed that FDA had approved 69 (52 percent) by the end of May 1979. The average approval time for these applications, which included 11 important drugs, was about 20 months—17 months of FDA time and 3 months of industry time. Only one application was approved within 6 months.
4. A number of important drugs were approved in some foreign countries in less time than in the United States. With the exception of Sweden, approval times in the countries GAO visited were considerably shorter.
5. Some of the 14 important drugs GAO selected were available earlier in the United States than in some foreign countries—all but 1 were available in at least one foreign country before they were available in the United States.
6. Both FDA and the drug industry contribute to the time it takes to approve new drugs. Industry officials pointed out, and GAO's review confirmed, that major factors affecting drug approval time were:

Imprecise FDA guidelines, subject to varying interpretations.

Scientific and professional disagreements between FDA and industry.

Slow or inadquate FDA feedback to industry and lack of promptness in notifying drug firms of deficiencies in applications.

Lengthy chemistry and manufacturing control reviews.

Limited time spent reviewing and uneven workload.

Incomplete new drug applications and industry's slow rate of resolving deficiencies.

7. Other factors contributing to delays include intense congressional and consumer scrutiny of the drug approval process, adversary relationships between FDA and the drug industry, and FDA's conservative approach to drug regulation.

Within the FDA, the GAO study focuses on the Bureau of Drugs, Dr. J. Richard Crout, director. In the Bureau the New Drug Evaluation Section and its Cardiorenal, Neuropharmacological, Metabolism and Endocrine, Anti-infective, and Oncology and Radiopharmaceutical Drug Products Divisions receiving most of the attention in this investigation. Part of the Information Systems section of the Bureau is also included in the investigation. (See Figure 1).

B. Actions of Other Congressional Committees

Today safety is a major concern in the approval of new drugs. The much cited Thalidomide disaster prompted passage of the 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act.

This made the pharmaceutical industry one of the most closely regulated industries. Citizens have not forgotten this drug disaster and in fact it was an event that promulgated greater concern for product and technology safety in many other areas as well. The Subcommittee also recognizes and acknowledges the many and valuable contributions that the Bureau of Drugs and the FDA have made in protecting the safety of the public by the thoroughness of its drug review and approval process to insure the safety and efficacy of drugs that are marketed.

However, no drugs are 100 percent safe. The requirement of both safety and efficacy has forced the FDA to assess the risks versus the benefits of a drug. In this respect, the FDA product approval process has become far more sophisticated than the approval process for most other products and also more cumbersome. This appears to be a reason for the slower rate at which drugs are being made available to the practicing physician.

The speed with which the agency approves new drugs for introduction into the United States has been a frequent target of criticism—both by drug manufacturers seeking to market the drugs and consumers either wanting to use them or to insure protection against possible unforeseen effects. Manufacturers have also charged that the slow drug approval process has had an adverse effect on innovative R&D in the pharmaceutical industry.

There is no question that the average time for approval of an NDA has increased—it was 14 months in 1963 and 26 months in 1977. The critical question is: Has this led to poorer health care for Americans? Another question is: What is our obligation as the most technologically advanced country in the world, to evaluate efficiently the safety and efficacy of these new agents and make them available as soon as possible to people who need them?

Drug Lag

"Drug lag" is a term used to describe the later point in time at which new drugs are approved in the United States compared to technologically advanced countries in Europe.

Congress has been aware of the drug lag but previous analyses have made little progress to alleviate it; 10 years after the 1962 amendments. Sen. Gaylord Nelson held hearings on "Competitive Problems in the Drug Industry" and supported the FDA position that there was no drug lag. However, the issue did not die there. At about the same time Dr. William Wardell (of the University of Rochester School of Medicine) published a series of analyses of the drugs available to the medical profession in Britain but not available in the United States. Wardell found that in nine different therapeutic categories, nearly four times as many new drugs (single chemical entities) became exclusively available in Britain than in the U.S. in the decade after 1962.

At first, the response of the FDA was a flat denial of a drug lag. In 1974, however, FDA testimony before the health subcommittee in Congress indicated that a significant number of drugs marketed in foreign countries were not available here. In the 10 years following the 1962 amendments, there were no approvals of new anti-hypertensive drugs and in the 5-year period between 1967 and 1972, there were no approvals of any new cardiovascular drugs. With such agents being approved abroad, physicians and pharmaceutical companies became concerned about the drug lag. Some companies apparently abandoned their research projects in these areas.

In the spring of 1979, the House Appropriations Committee and its Agriculture Subcommittee, Jamie L. Whitten (D-Miss.), Chairman, also addressed the issue of the drug lag. The FDA provided the committee a list of nearly 70 drugs that are currently marketed overseas but not available in the U.S. A major conclusion of the Committee was:

> The United States spends more on health care than most other industrial nations. Yet, the latest figures indicate that five nations have fewer deaths from cancer than the United States; 10 nations have a lower death rate from circulatory disease; 16 nations do a better job in keeping babies alive in the first year of life; and 17 nations have a higher level of male life expectancy. The Committee is concerned that these conditions may result partly because other countries have drugs available for use which the United States does not.

Today most of the public believes that the FDA makes available to them the best and most effective drugs known. But, more people are becoming aware through their relatives, friends and news media that drugs are available in other countries that are not available to them in the United States until months to years later. Delays in the approval of modern lifesaving therapies available elsewhere in the world has posed real problems for some of our sick. There have been numerous and well publicized cases where people have gone to Canada, Mexico, flown to England or had friends and physicians bring them drugs from abroad for the treatment of asthma, epilepsy and heart disease. This has forced citizens even to threaten class action suits to speed up the approval of drugs such as sodium valproate used in the treatment of epilepsy (U.S. trade name is Depakene.)

In terms of absolute number of new drugs introduced in the United States, this country appears to lag behind other countries. More significant, though, is the question whether the denial or delay of new drugs to the American patient has resulted in less responsive health care? Presently there is no definitive answer to this question. The FDA contends that few of the agents not approved in the United States represent therapeutic advances and that adequate substitutes are available here. Physicians and pharmaceutical manufacturers maintain that differences within classes of drugs can be important in offering the patient the most ideal treatment. Furthermore, the first drug approved in a given class of drugs is often not the optimum drug of that class. Some consumer groups on the other hand, feel that long approval times are equivalent to greater care in the evaluation of safety and efficacy of drugs.

New Drug Regulatory Reform Legislation

In addition to evaluating the FDA's efficiency under existing law the findings and conclusion of the GAO investigation should help to identify areas where new legislation might be needed to correct problems and therefore help Congress to decide among various proposals to reform the drug laws. In the 95th Congress the Administration's bills (H.R. 11611 and S. 2755) were discussed at length in hearings held by the Health Subcommittees in both the House and the Senate. With only technical changes the Administration's proposal was reintroduced in the 96th Congress as S. 1045 by Senator Kennedy on April 30, 1979, and as H.R. 4258 by Representative Waxman on

May 30, 1979. This bill is commonly referred to as the "Drug Regulatory Reform Act of 1979."

On May 3, 1979, Senator Kennedy also introduced a bill of his own, S. 1075, which resolves some of the issues raised last year in the hearings on the Administration bill. S. 1075 is not as comprehensive as S. 1045 and takes an approach of amending rather than making a total revision of the drug laws. (Major differences are, S. 1075 does not require full disclosure of all research data, does not implement a monograph system. See Appendix C).

Senator Schweiker also introduced a bill (S. 1138) on May 15, 1979. This bill would place more decisionmaking authority in the institutional review committee overseeing clinical research in their institutions. As such, these institutional review committees would share some of this authority with the FDA in an attempt to free up the early phases of clinical research.

Senator Kennedy held hearings on his bill in the Health and Scientific Research Subcommittee on May 17 and 18, and Mark up on June 25, 1979.

In the House not much specific activity has taken place on drug regulatory reform legislation. In addition to the Administration bill, a bill (H.R. 54) has been introduced by Representative Symms. The major provision of this bill would eliminate the testing of new drugs for effectiveness but still require safety testing. This bill has been introduced in previous years without much attention.

Legislative jurisdiction for drugs is with the Health and the Environment Subcommittee of the Interstate and Foreign Commerce Committee. Therefore recommendations arising from these SRT Subcommittee oversight hearings would be forwarded to the Health and the Environment Subcommittee for their consideration. This Subcommittee is not expected to take up action on new drug regulatory reform legislation before the fall of 1979.

C. Science, Research and Technology Subcommittee Hearings on "The FDA's Process for Approving New Drugs"

The major questions regarding FDA's process for approving new drugs which the subcommittee addressed are as follows:

1. Is the FDA's new drug approval process operating efficiently?
   Can the U.S. drug approval process be speeded up without sacrificing safety and efficacy?
   How?
2. How does the present rate of drug approval benefit or hinder health care in the U.S.?
   Does the U.S. new drug approval process really guarantee the consumer greater safety and efficacy or does it simply make patients wait longer for new effective drugs?
   Is there a drug lag and in which direction is the pendulum swinging?
   What is the significance of the drug lag and what are the important drugs involved?
3. Does the present drug approval process stifle innovation and productivity in the pharmaceutical industry?

The hearings addressing these questions were held on June 19, 21 and July 11, 1979. They were opened by Chairman Brown and co-chaired by Representative James Scheuer. To address the above questions, the subcommittee invited testimony by representatives of the GAO, the FDA, academe, medical and scientific associations, consumer groups, clinical researchers, physicians and industry. Below is a list of individuals who provided information for the hearing record:

June 19, 1979:

Gregory J. Ahart, Director, Human Resources Division, General Accounting Office.
William M. Wardell, M.D., Ph. D., Center for the Study of Drug Development, University of Rochester Medical Center.
J. Kiffin Penry, M.D., Director, Neurological Disorders Program, National Institutes of Health.
James Ferrendelli, M.D., Department of Neurology, Washington University Medical School.
Richard Masland, M.D., Professor Emeritus, Neurology Institute, Columbia University.

June 21, 1979:

Donald Kennedy, Commissioner, Food and Drug Administration.
F. Gilbert McMahon, M.D., Tulane University School of Medicine, representing the American Society for Clinical Pharmacology and Therapeutics.
Ray W. Gifford, Jr., M.D., Head, Department of Hypertension and Nephrology, Cleveland Clinic Foundation, representing the American Medical Association.
William Regelson, M.D., Medical College of Virginia.
Douglas P. Zipes, M.D., Indiana University School of Medicine.
Matthew Conolly, M.D., UCLA Medical School.

July 11, 1979:

Lewis Engman, President, Pharmaceutical Manufacturers Association.
W. Clark Wescoe, M.D., Chairman of the Board of Sterling Drug, Inc.
Lawrence C. Hoff, Executive Vice President for Worldwide Pharmaceutical Operations and Jacob Stucki, Director of Administrative and Support Operations of the Research Division, The Upjohn Company.
Robert S. Janicki, M.D., Vice President, Medical Affairs, and Richard W. Kasperson, Vice President Regulatory Affairs, Abbott Laboratories.
Fred Wegner, Legislative Representative of the American Association of Retired Persons and the National Retired Teachers Association.
Barbara Moulton, M.D.

ADDITIONAL STATEMENTS SUBMITTED FOR THE RECORD

Leonard S. Dreifus, M.D.
Stanley W. Jacobs, M.D.
John H. Lossing, M.D.
Beverly Shinn.
William C. Ristow.

ANALYSIS OF THE SCIENCE, RESEARCH AND TECHNOLOGY SUBCOMITTEE HEARINGS

I. THE U.S. "DRUG LAG"

Hearings on the "FDA's process for approving new drugs" cannot avoid the controversial issue of the "drug lag". The term "Drug Lag" has several definitions but for the purposes of concern to the subcommittee and its regard for the quality of health care of the American public, the most pertinent definitions of drug lag are:

The increased time to develop and approve new drugs in the United States compared to other technically advanced countries; or

The delay in introducing new drugs in the United States compared to other technically advanced countries.

Witnesses supported the existence of a drug lag in the United States today. Providing an independent assessment of this on-going and continuing controversy between FDA and industry, the GAO reported that 13 out of 14 important new drugs approved in the United States from July 1975 through February 1978 were available in Europe 2 months to 12 years earlier (Table 2). The drug approved first in the United States was a radiopharmaceutical agent, sodium oxide I–123. GAO also testified that other important drugs were delayed in the United States (Table 3). Four of these important drugs, alprenolol, ancrod, chenodeoxycholi acid and cyproterone, are not approved in the United States but have been available in Europe from 4 to 7 years. Mr. Ahart of the GAO further stated.

> In the sense that we do have a number of drugs classified or considered to be important that have been approved in other countries, that are not approved for use in this country and in the sense that a number of the drugs we looked at that have been approved in this country after they were available in other countries and took a longer time to approve, I would say it could be characterized as a drug lag.

The United Kingdom is often used as a comparison with the U.S. Discussing delays in the United States compared to the United Kingdom, FDA Commissioner Kennedy stated, "There is a very small difference between the United States and the United Kingdom . . . but the difference is very small." Dr. Kennedy said that delays are real for every developed medically sophisticated nation and that no developing nation has as many as half of the total drugs.

TABLE 2.—13 IMPORTANT DRUGS TOOK A LONG TIME TO APPROVE IN UNITED STATES

Drug	Use	FDA classification	First approval in Canada or Europe	Approval in United States	Delay
Phospholipids (Intralipid 10 percent)	Parenteral, nutritional agent	3–A–M	February 1964—Sweden	October 1975	1⅔ yr.
Propranol (Inderal)	Arrhythmias, angina, hypertension	6–A	June 1965—United Kingdom	November 1967	2½ yr.
			June 1965—United Kingdom	November 1967	2½ yr.
			October 1965—Switzerland	June 1976 [1]	11 yr.
			April 1969—United Kingdom.		
Amino acids (Aminosyn 7 percent)	Parenteral, nutritional agent	3–A	February 1966—Switzerland	December 1975	10 yr.
Sodium valproate (Depakene)	Epilepsy—Absence seizures including retinal	1–B	1967—France	February 1978	11 yr.
			August 1972—United Kingdom.		
			May 1972—Switzerland.		
Diazoxide (Proglycem)	Management of hypoglycemia	3–A	July 1969—Canada	May 1976	7 yr.
Somatotropin (Asellacrin)	Promote growth	1–A	May 1971—Sweden	July 1976 (15 mo) [2]	5 yr.
			1972 United Kingdom and Switzerland.		
Disopyramide phosphate (Norpace)	Cardiac arrhythmia	1–B	July 1972—United Kingdom	August 1977	5 yr.
Beclomethazone dipropionate (Vanceril Inhaler).	Chronic asthma	1–B	October 1972—United Kingdom	May 1976 (27 mo)	3½ yr.
Prazosin hydrochloride (Minipress)	Hypertension	1–B	October 1973—United Kingdom (6 mo)	June 1976 (40 mo)	2½ yr.
Danazole (Danocrine)	Endometriosis	1–B	June 1974—United Kingdom	June 1976	2 yr.
Protirelin (Thypinene)	Diagnosis of disorders of the hypothalmic-pituitary axis.	1–B	January 1975—United Kingdom	November 1976	2 yr.
Vidarabine (VIRA–A)	Herpes karatocon-junctivitis	1–A	August 1976—Canada	November 1967	3 mo.
Cimetidine (Tagamet)	Treatment of ulcers	1–A	November 1976—United Kingzom (2 mo)	August 1977 (13 mo)	9 mo.
Dobutamine hydrochloride (Dobutrex)	Treatment of cardiac decompensation	1–B	September 1977—United Kingdom	July 1978 (31 mo) [2]	10 mo.
Bromocryptine (Parlodel)	Endocrine disorders, Parkinson's disease, acromegaly.	1–A	1975—Switzerland	June 1978	3 yr.
			1976—Introduced United Kingdom.		

[1] New important indication for previously marketed drug.
[2] Length of time to review and approve the NDA is given in parentheses.

TABLE 3.—OTHER IMPORTANT DRUGS TAKE A LONG TIME TO APPROVE IN UNITED STATES

Drug	Use	Approval in Europe	Approval in United States	Delay
Alprenolol	Prevention of deaths after heart attacks	March 1976—Sweden	Not approved	4 yr.
Ancrod	Anticoagulant	1974—United Kingdom	Not approved	6 yr.
Chenodeoxycholic acid	Dissolve gall stones	1976—Switzerland	Not approved	4 yr.
Cyprotereone	Sexual hyperactivity, precocious puberty	1973—Germany	Not approved	7 yr.

Other witnesses did not agree with the Commissioner. Dr. Connolly, a specialist in the care of hypertension at the Royal Postgraduate Medical School in London until he emigrated to the United States 2 years ago, said:

> Since coming here and trying to practice clinical medicine as I did it in England, I have had an increasing sense of frustration. Quite frankly, I'm appalled at the drugs which are not available for me to use here . . . There can be no doubt whatever that the drug lag is a real phenomenon, and any attempt to parlay one's way around this is pure sophistry.

Dr. Masland, former Executive Director of the Commission for the Control of Epilepsy and its Consequence (which was created by the Congress) discussed the increasing delays being experienced in the U.S. development of antiepileptic drugs.

> Comparing the United States with the United Kingdom, we note there is no (antiepileptic) drug which has been introduced into the United States before the United Kingdom since 1964. There are nine drugs, introduced first in the United Kingdom and, of these, four are still not available in the U.S. (see section II.2.a).

Furthermore, the Subcommittee notes that of the important drugs GAO identified, 7 were approved first in the United Kingdom 9 months to 5 years before they were available in the United States (see Table 2) and three other drugs were also approved in the United Kingdom before the U.S. (Of these drugs GAO found as important, only NaI^{123} was approved first in the United States during the period GAO examined).

Dr. Wardell, the major academic investigator dealing with this issue, testified;

> . . . there is no doubt that for marketed drugs and approved therapeutic indications, the U.S. lags greatly, in the sense that new drugs are usually available abroad either exclusively or much earlier, and for a wider range of conditions.

Wardell notes:

> Even when a drug has been developed by a U.S. firm it is often late in its history that it becomes available in the U.S.—for example, the United States was the 15th country in which the anti-inflammatory drug indomethacin was marketed and also the 15th for the diuretic ethacrynic acid and the antidepressant protriptyline; the 22nd country for the anti-inflammatory drug fenprofen; the 39th country for the first oral cephalosporin, cephalexin; and the 40th country for the anti-tubercular antibiotic capreomycin.

> When an advance is originated by a foreign-owned firm or institution, the United States is usually even further down the list. It was the 32nd country to approve the important anticancer drug adriamycin; the 41st country to approve the antimania drug lithium carbonate; the 51st country to approve the antitubercular drug rifampin; the 65th country to approve the antiallergic drug cromolyn sodium; and the 106th country to approve the antibacterial drug co-trimoxazole.
>
> Even when a drug is finally approved for U.S. marketing, the indications for its use are often restricted and out-of-date.

Dr. Ray Gifford, representing the American Medical Association testified:

> In recent years, physicians have noticed a disturbing trend that drugs ultimately approved in the U.S. as major treatment break-throughs—drugs that subsequently become the drugs of choice—have been available in other countries for significant periods of time prior to U.S. marketing. As a practicing physician, I cannot understand anybody that says we don't have a drug lag.

Other physicians involved in drug research and development also supported the existence of a drug lag as did members of the pharmaceutical industry. As noted earlier, consumer activists do not deny a drug lag but equate it to greater consumer protection.

There are drugs that have been approved first in the U.S. In comparisons with five other countries (England, France, Germany, Italy, and Japan) the FDA states that in the 17 year period (1962 through 1978) there were 139 drugs approved first in the United States. Of these 10 were considered by the FDA to be important therapeutic gains: (Category A drugs):

Tromethamine
Bephenium Hydroxymaphthoate
Candicidin
*Technetium Tc 99m Albumin Microspheres
*Selenomethionine Se/5
Vifilcon A
*Xenon Xe 133
Beta-Carotene
*Sodium Iodide, I 123
Calcitriol

According to the FDA 48 other drugs classified as modest therapeutic gains (Category B drugs) were also approved first in the United States bringing the total (A and B drugs) to 58 over the 17 years (see Tables 4, 5 and 6 for FDA drug classification systems).

TABLE 4.—*FDA IND/NDA drug classification system—chemical types**

Type 1.—New molecular entity—i.e., the active moiety is not yet marketed in the United States by any drug manufacturer either as single entity or as part of a combination product.

Type 2.—New salt—i.e., the active moiety is marketed in the United States by the same or another manufacturer but the particular salt or ester is not yet marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product.

Type 3.—New formulation—i.e., the compound is marketed in the United States by the same or another manufacturer, but the particular dosage form or formulation is not.

Type 4.—New combination—i.e., contains two or more compounds which have not previously been marketed together in a drug product by any manufacturer in the United States.

Type 5.—Already marketed drug product—i.e., the product duplicates a drug product (the same active moiety, same salt, same formulation, or same combination) already marketed in the United States by another firm.

Type 6.—Already marketed drug product by the same firm—used primarily for new indictions for marketed drugs.

*These types are not mutually exclusive, since a new formulation (Type 3) or a new combination (Type 4) may also contain a new molecular entity (Type 1) or a new salt (Type 2). In such cases, both numbers would be included in the overall classification number for the drug. For example, a new molecular entity representing an important therapeutic gain would be classified 1A; if the new entity were also in a new controlled-release formulation, it would be classified 13A.

TABLE 5.—*FDA IND/NDA drug classification system—Therapeutic potential**

Type A.—Important therapeutic gain—i.e., drug may provide effective therapy or diagnosis (by virtue of greatly increased effectiveness or safety) for a disease not adequately treated or diagnosed by any marketed drug, or provide improved treatment of a disease through improved effectiveness or safety (including decreased abuse potential).

Type B.—Modest therapeutic gain—i.e., drug has a modest, but real, potential advantage over other available marketed drugs—e.g., greater patient convenience, elimination of an annoying but not dangerous adverse reaction, potential for large cost reduction, less frequent dosage schedule, useful in specific subpopulation of those with disease (e.g., those allergic to other available drugs), etc.

Type C.—Little or no therapeutic gain—i.e., drug essentially duplicates in medical importance and therapeutic usage one or more already marketed drugs.

Type D.—Special situation—i.e., drug has decreased safety or effectiveness compared with alternative marketed drugs, but also has some compensating virtue (e.g., provides treatment for patients who do not respond to or are intolerant of alternative drugs).

Type E.—DESI/OTC Claim—i.e., IND or NDA is intended to support a "less than effective" claim under DESI or OTC review.

*These types are mutually exclusive. Only one of these letters may be included in the overall classification number.

TABLE 6.—*FDA IND/NDA drug classification system—Other categories**

Type M.—Drug already *marketed* in a foreign country.

Type P.—A very important feature of application is the *packaging* or container, not the drug itself.

Type R—Drug is subject to specific unique conditions of approval (e.g., additional studies) outlined in approvable or approval letter for NDA.

Type S.—Application is *sensitive* by virtue of wide publicity, congressional interest, unusual request from firm, etc.

Type T.—Important problem in *toxicity*—e.g., carcinogenic in animals.

Type U—Drug is likely to be *used in children.*

*These types are not mutually exclusive. All appropriate letters would be included in the overall classification number.

Direct comparison of FDA data with GAO data is difficult. FDA includes radiopharmaceuticals(*) which are not reported in the data from other countries. FDA and GAO also use different sets of countries and different periods of time. The exact magnitude of the drug is difficult to quantify because it is in a state of flux and because of the lack of a broad base of directly comparable data in regard to the countries in which drug is available, the importance or significance of the drug, indications for its use, and the period of time over which the comparison is made.

The exact magnitude of the drug lag is not the critical issue. The Subcommittee finds there is a common consensus that there is a drug lag of considerable magnitude. Examples of significant drugs which the subcommittee found to be delayed in the United States are discussed in the next section.

The Subcommittee concludes there is a "drug lag" in the United States today, particularly in regard to important drugs, i.e., those drugs offering important or modest therapeutic gains, as contrasted with drugs offering little or no therapeutic gain and drugs duplicating already marketed drug products.

A more significant question to address however is: What is the impact of the "drug lag" on health care in the United States?

II. HEALTH IMPACT OF THE "DRUG LAG"

For the U.S. public, the drug lag has the potential for both benefit and harm. Benefits may arise from longer and more thorough testing of a drug before marketing to better establish safety and efficacy. Harm can arise because delays in the approval of a drug deprive the sick from medicines which are lifesaving, reduce suffering, and/or help maintain a productive life. Therefore, any protection conferred by delaying the introduction of new drugs must be weighed against the therapeutic losses incurred by delaying effective new therapies.

FDA states their function is to regulate the introduction of new technologies (drugs) and that regulation automatically slows down the introduction of new technologies. Consumer activists have developed a high level of confidence in FDA. This apparently results from their thinking that FDA's slower approval process guarantees consumers that drugs approved for the U.S. market are more likely to be safe and effective than drugs approved sooner in other technically advanced countries. This is not supported by major conclusions of the GAO investigation. In fact GAO testified that:

The approval of new drugs in the U.S. takes longer than it should. The statutory 180-day review time is generally not met. Approval time for NDAs submitted in 1975 was about 20 months (based on 68 approved NDAs out of 132 filed).

The lengthy approval times for important drugs deprive the general public of the therapeutic advances of such new drugs without identifiable safety benefits.

Lengthy approval times can add substantially to the cost of developing drugs.

A. Safety Benefits Do Not Justify Lag

In regard to drug safety, everyone immediately thinks of the Thalidomide tragedy, particularly for European countries. It is important to note that the FDA never approved its use in the United States, sparing the United States from far more than the nine cases of birth defects (phocomelia) experienced in clinical trials when the drug was given to 3,879 U.S. women of childbearing age.

The subcommittee thinks it is important to judge the approval system nearly two decades later on the basis of the drugs approved since Thalidomide. Thalidomide was a serious tragedy not to be minimized, but it must also be remembered that the Thalidomide tragedy resulted in extensive changes in drug laws here and abroad. Here Thalidomide prompted passage of the Kefauver-Harris drug amendments of 1962. These amendments paved the way for more extensive FDA requirements regarding the safety and efficacy of drugs. Technically advanced countries in Europe have since changed their laws to require more stringent safety and efficacy data in the approval of new drugs.

The GAO stated that the more expeditious European drug approval process is not explainable on the grounds that their safety and efficacy

standards are lower than ours. Mr. Lewis Engman, PMA president, states ". . . there is no evidence that shorter approval times in other countries has resulted in health hazards."

This is not to say there have been no drug safety problems in Europe since Thalidomide. A number of drugs which were approved in Europe since Thalidomide, but which were removed from the market because of safety problems, were discussed by Drs. Moulton and Wardell (Table 7). In some cases, there may be questions raised about whether the problems, which resulted in the removal of the drugs from the market place, were drug related. None of these drugs were approved for marketing in the U.S.

TABLE 7.—DRUGS REMOVED FROM THE EUROPEAN MARKET

Drug	Use	Major adverse reaction
Practolol (United Kingdom, 1969)	Antihypertensive	Severe conjunctivitis (withdrawn, 1975)
Medihaler-Iso Forte (stronger form of isoproterenol than approved in the United States).	Antiasthmatic	Deaths (withdrawn).
Aminorex (Switzerland, 1965)	Appetite suppressant	Pulmonary hypertension (withdrawn, 1968).
Ibufenac (United Kingdom, 1966)	Analgesic, anti-inflammatory	Jaundice-hepatotoxicity (withdrawn, 1968).
Benziodarone	Antiangina	Jaundice (withdrawn, 1964).

The most significant of these examples appears to be practolol. Several witnesses testified on problems regarding this drug.

For example, William Wardell noted:

> Most of the arguments that seek to deny the drug lag problems are based on the allegation that the new-drug toxicity that the U.S. has avoided by the drug lag is of very large size; there has even been a claim of benefit to the United States in the form of a "death lag". It is ironic that practolol, the drug chosen to illustrate this connection, has, despite its known toxicity, an extremely high benefit-to-risk ratio when used to prevent heart attacks and coronary death. If it were available and used optimally in post-myocardial infarct patients in the U.S., this drug could be saving 10,000 to 20,000 lives a year, with a degree of toxicity that would now be small and controllable, and highly acceptable compared with the lifesaving benefit provided. To call the practolol example a "death lag" is a cynical inversion of the facts.

Matthew Connolly stated regarding studies on beta blocking drugs:

> There have been three studies in Europe, two in Sweden, and one in England, using two beta blocking drugs practolol and alprenolol in treating patients who have survived a first heart attack. In all three studies, it has been shown there has been a substantial reduction in mortality in patients treated with those drugs . . . In this country (United States) each year, some 300,000 to 600,000 patients die from coronary artery disease.
>
> Now, supposing all these patients had been put on practolol, and let us suppose that the data obtained in the English practolol study could be extrapolated to the American population, this might mean that each year death might have been pre-

vented in nearly a quarter of a million people, many of whom are still quite young. This still awaits proof, but what I think we must ask is whether by being so rigid and excluding so many drugs we aren't really paying a price that is really almost beyond imagining.

Now, practolol has been used to provide justification for the rather restrictive attitudes of the FDA, and they say look what it did in England, produced those terrible eye symptoms, produced blindness, ear troubles, peritonitis, and of course, one has to admit in honesty that this kind of problem did arise. But I think we need to look at the frequency with which it happened, too.

In England at the time practolol was withdrawn we had 250,000 patient years of experience with that drug. . . . At the time it was withdrawn 619 validated cases of adverse reactions to practolol had been discovered, including 20 cases with severe conjunctivitis leading to impaired vision. To the individuals involved this was a tragic outcome.

But I think all the time the discussion this morning has come back to the risk-benefit ratio. We need to look at what the risks are, of course, but we need to look honestly at what the benefits are.

If serious safety problems surface after marketing in Europe, a drug will not be approved in the United States. The United States was apparently spared some of the toxicity problems which developed in Europe simply through FDA's routine administrative process, during which time the adverse effects of drugs already on the market in Europe became apparent. Thus U.S. non-approval may be more accidental than deliberate in the sense that it can be based on European post-marketing experience rather than critical insight into the information and questions raised by FDA regarding the NDA. If the United States relies on broad post-marketing surveillance for experience in Europe in order to decide whether to approve a new drug, the American patient will generally be protected from unforeseen toxic effects by a slower U.S. drug approval process. Concurrently, however, many American patients will forgo the benefits of new medical advances already available in other countries because of delays in the FDA drug approval process. This also raises a number of ethical questions surrounding the rate of U.S. new drug approval as compared with European countries?

In the above cases of drug problems in Europe (Table 7) the FDA did have the benefit of being able to rely on wide human clinical experience after the drug was marketed in Europe.

Although witneses did not discuss drug safety problems in the United States, it is easy to find that the slower U.S. drug approval system has not entirely avoided them. This is because animal testing provides at best limited assurances on the safety of a drug in man. Low incidences of adverse effects (less than one per thousand) can not reasonably be detected in clinical studies. Some recent drugs which developed serious safety problems to warrant their removal from the market are tienilic acid (Selacryn), and azaribine (Triazure) (Table 8). The best way to detect these problems is through effective post-marketing surveillance.

TABLE 8.—SOME DRUGS RECENTLY REMOVED FROM THE U.S. MARKET

Drug	Use	Major adverse problem
Tienilic acid (Selacryn) (approved May 1979).	Antihypertensive with uricosuric properties (diuretic).	Liver damage and possibly death (withdrawn).
Azaribine (Triazure) (approved February 1975).	Psoriasis	Thromboembolism and death (withdrawn August 1976).

B. Need for Post-Marketing Surveillance

Implementation of post-marketing surveillance procedures in the U.S., similar to those already in use in European countries, would appear to offer an opportunity not only to reduce significantly the time and delays in drug development and testing (IND) phases but also obtain longer-term follow-up and currently not readily available information on possible adverse reactions that may not be readily observed, due to insufficient patient numbers in the clinical trial phases (II and III) of the IND process.

According to William Wardell, improved post-marketing surveillance techniques would asist FDA in its decision making, and ". . . "might actually allow a reduction in the length of Phase III trials. This would be in contrast to the inexorably-increasing spiral of regulatory cost and time requirements we now see."

In response to additional questions requested by the Subcommittee, the GAO indicated:

> The postmarketing surveillance systems of the United Kingdom and the United States are based primarily on spontaneous reporting from physicians, hospitals, and drug firms. However, there are key differences in the extent of physician participation. . . .
>
> Virtually all the foreign countries we visited, including the United Kingdom, have national health care systems with governmental controls which may facilitate the review of medical documents by government authorities, thus making the reporting of adverse reactions more likely. The United Kingdom has a formal followup procedure for adverse drug reaction reports and is able to protect the confidentiality of the reporting source. . . .
>
> The United Kingdom officials also attribute some of their success with physician participation to feedback of information about adverse drug reactions, which has generated an awareness of drug-related events. . . .
>
> . . . The usefulness of FDA's present system is affected by the reluctance of some physicians to report drug reactions because of a perceived fear of possible malpractice suits.

The GAO noted that:

> In March 1974, we reported to the Congress that FDA's adverse drug reaction reporting system had not been used adequately to regulate drugs and was deficient in many respects. For example, FDA (1) received only a limited number of adverse reaction reports, (2) did not always obtain additional information needed to evaluate reports received, (3) did not store centrally all information available with-

> in FDA, and (4) did not send complete information to the regulatory divisions. FDA has since centralized its adverse drug reaction reporting system in one unit in its Bureau of Drugs.

The GAO indicated further that proposals from Senator Kennedy and the Administration currently under consideration may offer more favorable alternatives to the present system of post-marketing surveillance.

> Under the proposals, drug manufacturers would be required to establish and maintain a system for collecting and reporting information to FDA on adverse drug reactions. This system should provide FDA with a more intensive means of obtaining information on drug experience that is not presently available to FDA. If this system is effectively implemented, FDA would have a better means of identifying more quickly problems with marketed drugs and to consider the need for regulatory action against such drugs to protect consumers from unnecessary harm.

Such proposals may also offer prospects for encouraging greater innovation in and investment of R. & D. resources within the pharmaceutical industry, of expediting the IND phases, and reducing FDA's regulating requirements during early phases of new drug testing.

C. Therapeutic Losses for America's Sick

There is no question there are a number of drugs rated as important by the FDA and the medical profession which have not been available to American patients for months to years after they have been available in European countries. The GAO focused on 13 drugs which FDA classified as important; nine of which were delayed 2 months to 12 years and four of which have now been delayed over four years and still are not available (Table s 2 and 3). GAO concluded that these delays deprive the general public of therapeutic advances of such new drugs.

Testimony of practicing physicians, clinical researchers and industry representatives uniformly supported this conclusion.

Dr. Wardell concluded:

> Our analyses of the therapeutic implications of the drug lag show that British patients clearly gain by having effective new drugs available sooner, while the toxicity attributable to these new drugs is relatively small, and certainly not enough to outweigh the benefits. The U.S. has thus, on balance, lost more than it has gained by an ultraconservative policy. Some areas in which the lag has been most marked and therapeutically significant include therapies for cardiovascular, respiratory, central nervous system, and gastrointestinal diseases.

Dr. Gifford said:

> This trend (drug lag) is especially troubling when the drug provides a therapeutic break-through over the other available treatment modalities. Even when the improvement is only incremental, failure to have such improvements avail-

able means there is a therapeutic detriment to patients through the limitation of the armamentarium available to physicians to treat illness and injury.

And Dr. Regelson stated:

> We have to understand that crippling illness or unnecessary deaths occur because of drug availability delay. The loss of countless lives cannot be justified by the argument that a few people's lives may be at risk! It is prudent that we must see the issue in terms of human rights for the lethally ill or seriously crippled. It has to be seen as the "right to risk", the "right to receive", and the "right to life," versus the acceptance of the status quo, which can guarantee death, despair and increasing debility.

A contrary opinion was expressed by consumer activists. Dr. Moulton:

> believes there is ". . . a great deal of unsubstantiated opinion testimony that FDA delays cause loss of life, but no factual proof." She thinks ". . . in all likelihood more lives have been lost than saved by the release in other countries of the very drugs which are usually cited in an attempt to prove that FDA restricts lifesaving drugs at the cost of lives."

The subcommittee focused on lost benefits from drugs particularly for the treatment of cardiovascular diseases, our nation's number one killer; and neurological diseases, namely epilepsy. Numerous examples of significant therapies denied for some time to the American patient for treatment of other diseases were presented at the hearings.

1. CARDIOVASCULAR DISEASES

The need for better treatments for cardiovascular disease is obvious. Cardiovascular diseases are the number one killer in the United States today. These diseases account for over fifty percent of all deaths—more than twice as many deaths as cancer.

(*a*) *Antihypertensives*

Since 1963 most new antihypertensive drugs have been marketed first outside the United States. This is accentuated because no hypertensives were approved in the United States for an entire decade, from the introduction of pargyline and methyldopa in 1963 to the introduction of diazoxide in 1973.

Meanwhile numerous agents including the important new class of beta-blocking agents continued to be approved abroad.

There can be no argument that drugs that are effective in major hypertensive crisis are lifesaving with, diazoxide (Hyperstat) being most effective. This drug has only been available to American physicians for six years, even though it had been under investigation for over 10 years before it was approved. Diazoxide had been marketed in the U.K. for almost a year before it was approved in the United States.

(i) *Beta-blockers.*—These drugs achieve their action by blocking the action of adrenaline-like compounds in body tissues with beta-

receptors. The beta blocking drugs are a major advance in the treatment of hypertension, coronary heart disease, certain abnormalities of cardiac rhythm, thyroid diseases and several other conditions. After long delays the only members of this rather diverse group of drugs available in the USA are propranolol (Inderal) and metoprolol (Lopressor). A number of other drugs of this class which have advantages to certain patients are available in European countries.

The long delay which has occurred in the introduction of new beta blockers to the U.S. market has two components. The first is the usual slow regulatory review process. The second has been the ban which was imposed on the clinical testing of all new beta blocking drugs because of apparent tumor producing activity in animals by one of them. (The very first beta-blocker, pronethalol, had also been abandoned because of the development of tumors in mice, though subsequent testing was unable to reproduce this effect.) This blanket decision was taken despite the fact that propranolol had been in use in man, often in very large doses, for over a decade without evidence of human tumor development. This decision has been a significant factor in the delay in appearance of several beta blocking drugs.

Propranolol (Inderal) was approved for the treatment of hypertension more than 7 years earlier (April 1969) in the United Kingdom and 11 years earlier (October 1965) than in the United States. This drug at the time of its introduction, represented a most important advance in treatment of high blood pressure. It was approved for the treatment of arrhythmias and angina more than 2 years earlier (June 1965) in the United Kingdom than in the United States (November 1967). Although still the most widely used beta blocker, it does have some drawbacks. One of these is that it not only blocks the effect of adrenaline-like compounds in the heart, it also does so in the lungs. This makes it impossible to use in patients with asthma.

There have been numerous attempts to develop cardioselective agents, which do not affect the lungs, and 3 or 4 of them now exist. Even though their cardioselectivity is not absolute, these agents are useful in asthmatic patients who have angina or hypertension.

Metoprolol (Lopressor) was approved for the treatment of hypertension in the U.S. in August 1978, three years after its introduction in the United Kingdom. It has cardioselective properties. FDA classified it as a modest therapeutic gain (B) as a antihypertensive beta blocker.

Alprenolol was approved in Sweden more than 3 years ago for prevention of death after heart attacks. It is not approved in the U.S. It is one of only a few beta blocking drugs shown to reduce mortality in patients who survive a heart attack. Another is practolol. It is interesting to note that the only thing these two agents have in common is that they are beta blockers which possess a pharmacological property called intrinsic sympathomimetic activity (ISA).

The potential importance of this observation, which awaits confirmation, is that hypertension is a major cause of heart attacks. Between 300,000 and 600,000 Americans die each year from heart attacks. In the practolol study in England, mortality was reduced by 36 percent. Wardell conservatively calculated, if practolol were available and used optimally in post-myocardial infarct patients in the United States, this drug could be saving 10,000 to 20,000 lives a year, with a degree

of toxicity that would now be small and controllable, and highly acceptable compared with the lifesaving benefit provided.

According to FDA, INDs were submitted for alprenolol in 1966 and 1971 for its use as an anti-arrhythmic agent and for the treatment of angina pectoris. Carcinogenic studies in animals revealed an increase in numbers of tumors; however, fewer were found in a second study. Clinical studies were withheld in 1971 pending resolution of animal carcinogenicity problems which FDA thought were common, at that point, to beta blockers. This IND was voluntarily discontinued in 1973 by the firm, the reason given being other research prorities and commitments.

It appears heart attack victims in the United States may never have alprenolol. We cannot tell if all Americans who died of heart attacks last year had been on a beta blocker with ISA that nearly a quarter of a million would be alive today? But the question which demands an urgent answer is, are we denying substantial benefit, even life itself, to thousands, if not hundreds of thousands of U.S. citizens by delaying the introduction of alternative drugs such as alprenolol? It is hard to believe that we are not. Statements about benefit outweighing cost must be viewed in this light.

Atenolol has considerable cardioselectivity and a long duration of action. The IND was filed in 1973 and long term clinical trials began in the United States in late 1978. An NDA was filed with the FDA in December of 1978 and has not yet been approved.

Oxprenolol also has the ancillary property called intrinsic sympathomimetic activity (ISA). According to the FDA it is being studied for its cardiac antiarrhythmic as well as its antihypertensive properties.

An investigational application was originally filed in 1969 by a firm licensed by the parent company. Animal studies, performed according to FDA guidelines for carcinogenic trials, have been completed and the drug has been cleared for clinical trials which are now underway.

Pindolol also has the property of ISA. According to the FDA this beta-adrenergic blocking agent has been studied for cardiac antiarrhythmic properties under IND's filed in 1968 and 1969. The firm performed animal carcinogenicity studies and explored other toxicity problems. The carcinogenicity studies cleared pindolol for long-term clinical study. The drug is under active investigation at this time in the United States.

Labetalol is the only combined alpha and beta receptor blocking agent in clinical use at the present time. It is especially valuable in patients whose blood pressure is difficult to control. It is well tolerated with little in the way of a troublesome drop in blood pressure on standing. This drug has been used continuously in patients for periods of up to 7 years in England. It was introduced in the United Kingdom in 1977, and is now available on prescription to all patients in the United Kingdom. The U.S. IND for treatment of hypertension was filed in 1975. The required long-term animal studies were submitted in 1978 and clinical studies of greater than 30 days duration were permitted in early 1979. FDA classifies Labetalol as a modest therapeutic gain (B). Clinical trials have only recently begun in the United States and approval will be years away.

(ii) *Vasodilators.*—Vasodilators are a class of drugs which dilate or open up peripheral arterioles. They are of great value in treating particularly the most resistant forms of high blood pressures.

Prazosin hydrochloride. (Minipress) an application for prazosin hydrochloride was submitted for approval in the United States in February 1973, and in the United Kingdom in April 1973. This drug was approved for use in the United States in June 1976 or 40 months after the NDA was submitted and in the United Kingdom in October 1973 or 6 months after application was submitted.

Minoxidil (Loniten) is one of the most potent vasodilators. It has been used to treat the most severe forms of hypertension with good results. It has been described as an alternative to the drastic step of surgical removal of both kidneys in gaining control of refractory hypertension (Pettinger and Mitchell, 1973), clearly a desirable advance. In October 1979 it was approved in the U.S. FDA classifies it as a modest therapeutic advance (B) in the treatment of severe hypertension.

Clonidine (Catapres) became available in the U.S. in 1974.

(iii) *Diuretics.—Ethacrynic acid* (Edecrin). See Furosemide.

Furosemide. (Lasix): Ethacrynic acid and furosemide are known as loop diuretics because they work in the area of the kidneys where large amounts of sodium is reabsorbed. Because they prevent this sodium reabsorption they are very potent diuretics. Ethacrynic acid and furosemide are the most potent diuretic agents available in the U.S. They are the only diuretics that are effective for patients with impaired kidney function. Often these drugs make it possible to control hypertension in patients with kidney disease when the blood pressure is resistant to other combinations of available drugs. British patients had the advantage of these two potent diuretics for two years before American patients did. In fact the United States was the 15th country in the world to approve ethacrinic acid.

Amiloride hydrochloride. This is a potent potassium-sparing diuretic agent for which an IND was filed in 1964. This drug is for use as a diuretic in patients who were unable to conserve potassium. According to FDA, a NDA was subsequently submitted in 1968 and found later that year to be not approvable. The studies were based on an inappropriate patient population, and there were some deaths. Not all of the latter were attributed to the drug directly but 15 were attributable to hyperkalemia. FDA believes acceptable alternatives in this potassium-sparing diuretic class are marketed in the United States, that is, triamterene and spironolactone. The original commercial sponsor has filed a new IND, carried out new clinical studies, and expects to file another NDA shortly.

(iv) *Other antihypertensive drugs not available in the United States.*—Bethanidine belongs to a group of drugs known as the adrenergic neuron (sympathetic) blocking drugs. It has unique advantages for a certain select group of severely hypertensive patients. Only one of this family of drugs is available here—a drug called guanethidine. Of all the members of this group, guanethidine is perhaps the hardest to use. Because of the way the body handles it, it may take up to three weeks for the maximum effect of any dose or change of dose to become apparent. This makes adjustment of therapy very difficult.

If an overdose situation should arise, or if the patient moves to a hotter climate where his blood pressure is more likely to fall to low levels, again it may take 3 weeks for the effect of reducing the dose to be felt maximally, and in the meantime the patient may be troubled by feelings of weakness, faintness or even fainting, on standing or after exertion.

A further problem associated with guanethidine is the sometimes explosive diarrhea which it may produce, a symptom which can be severely disabling.

Bethanidine, in contrast, is a more flexible agent. Its duration of action is brief so that dosage adjustments can be made rapidly. If faintness at night or at any specific time of day is a problem, the scheduling of doses can easily be altered. It does not cause diarrhea. Bethanidine was approved in the United Kingdom in 1963, and has also been available in Japan, Germany and other countries for 15 years. It is now available in every country in the world (including Canada) except the United States. An NDA was submitted in the United States in December 1974. Despite its proven human efficacy and safety it is still excluded from the American market because the FDA insists on further animal toxicity testing. One company has already abandoned attempts at marketing this drug and a second may do the same.

Bumetamide and Debrisoquine are other diuretics whose availability have been delayed.

(*b*) *Heart failure*

Dobutamine hydrochloride (Dobutrax) is a drug used for treatment of cardiac decompensation, a form of heart failure. It was approved in July 1978, 31 months after it was initially submitted for approval. Dobutamine was approved for use in the United Kingdom in September 1977. FDA classifies it as a modest therapeutic gain (B) for inotropic support in cardiac decompensation due to deprived contractility.

(*c*) *Antiarrhythmic agents*

In the field of antiarrhythmic drugs only two drugs were approved in the United States from 1962 to 1975 (after substantial lags in both cases).

Disopyramide (Norpace) was synthesized in 1954 and its phosphate salt, finally approved for general clinical use, has been studied in the United States since 1965. Disopyramide base is commercially available in Europe. It was approved in the United Kingdom (July 1972) more than 5 years earlier than in the United States. (August 1977).

Other antiarrhythmic drugs available in Europe but not approved in the United States are:

Verapamil, a papaverine derivative and slow-channel blocker, was first marketed in Germany in 1962 and investigated as an antianginal drug in the United States shortly thereafter. However, clinical trials in the United States were stopped when early toxicologic studies in beagle dogs suggested that verapamil at large doses administered for a year may have caused cataracts. Subsequently, it was established that the lens protein of beagles differed from other species and that verapamil-induced cataracts appeared to be a species-specific occurrence. No lens changes or eye problems definitely attributable to verapamil

have occurred in other animals or during 15 years of worldwide clinical experience. Therefore, very recently, clinical investigation of verapamil in the United States has been renewed and the drug is now being used orally and intravenously at several centers. It is available clinically throughout much of the rest of the world.

Amiodarone, a benzfuran derivative with an antagonistic effect on sympathetic nerve action, has been used clinically in Europe and South America for at least 2 years.

Aprindine, an antiarrhythmic agent with prominent local anesthetic effects, was developed and used initially in Belgium. It is available clinically throughout most of Europe and is being evaluated as an investigational agent in the United States.

Ethmozin, is a phenothiazine derivative synthesized at the Institute of Pharmacology of the USSR Academy of Medical Sciences in 1964. Clinical trials have been carried out in the Soviet Union and investigational use of the drug clinically has begun recently in the United States.

Encaimide is another antiarrhythmic drug available in other countries.

Mexiletine is an orally active drug similar in its spectrum and pharmacologic properties to lidocaine. It was first used as an antiarrhythmic agent in 1969, and was approved for clinical use in Europe and Great Britain. In Britain it was introduced in 1977. It has been under evaluation as an antiarrhythmic agent in the United States since 1977 but according to the FDA there has been relatively little, and only very early activity to date. FDA classifies it as a modest therapeutic gain (B) and states that an orally active agent with properties similar to lidocaine would be an important drug.

Tocainide, an analog of lidocaine, is now undergoing clinical trials in the United States. It differs from lidocaine in that it can be taken orally because it lacks two ethyl groups that contribute to lidocaine's first-pass hepatic degradation after oral administration.

Hundreds of thousands of people are affected with cardiac arrhythmias, Dr. Zipes, a noted expert on antiarrhythmic drugs, estimates that many lives might be saved if we had these other drugs available in the United States.

> These seven antiarrhythmic agents (not including encamide), plus several new beta adrenergic receptor blocking drugs, bretylium and other compounds still in early testing stages, represent promising advances for the therapy of cardiac arrhythmias. Although pacing and surgical ablation techniques have resulted in spectacular successes for some patients with certain types of drug-resistant tachyarrhythmias, the vast majority of patients must be treated medically because of the large number with symptomatic and even life-threatening cardiac arrhythmias. If the tachyarrhythmia does not respond to procainamide, quinidine, propranolol or diphenylhydantoin, or if the patient cannot tolerate these agents, other antiarryhthmic drugs must be available to the practicing cardiologist. As more effective antiarrhythmic agents with fewer side effects are developed, the need for pacing and surgical approaches will diminish.

(*d*) *Antianginal drugs*

The situation regarding antianginal drugs is different from antiarrhythmic drugs. The usual array of nitroglycerin-like preparations are available in the United States. Surgery, though expensive, can also be successful for patients with drug resistant angina. But Europeans have available a variety of other drugs as well as beta adrenergic receptor blocking agents with cardioselective activity.

Beta blockers have been discussed under antihypertensive drugs. In the treatment of angina these drugs have not been shown to offer a great deal of advantage over propranolol, which lacks cardioselective action, but is now available in the United States.

Nifedipine is available in Europe but not the United States. It was introduced in the United Kingdom in 1977. FDA classifies it as a modest therapeutic gain (B).

Verapamil is available in Europe but not the United States.

Both Nifedipine and Verapamil appear effective for treatment of "variant or Prinzmetal's angina". This anginal syndrome is often related to coronary spasm and may not respond to conventional drugs, nor be treated by surgery. It is primarily in this area that United States physicians are limited at present.

(*e*) *Anticoagulant drugs*

Ancrod is a proteinase from the venom of the pit viper (agkistrodon phosdostoma) which has been marketed since 1974 in the United Kingdom and used as an anticoagulant to prevent or treat blood clots. An IND was submitted to the Bureau of Biologics in 1970 by the Abbott Laboratories. The IND remains active.

2. NEUROLOGICAL DISEASES

(*a*) *Antiepileptic drugs*

Epilepsy is the second most prevalent disorder affecting the central nervous system; only stroke occurs more often. More than 2 million Americans suffer from some degree of epilepsy. The seizures of more than half of these individuals have been controlled or improved with the antiepileptic drugs, but at least 500,000 Americans with epilepsy look with hope to the development of new, more effective antiepileptic drugs.

Significant differences between Britain and the U.S. have existed in the drugs available for treatment of epilepsy. There is no antiepileptee drug which has been available in the United States before the United Kingdom since 1964. Since then nine drugs were introduced first in the United Kingdom and, of these, four are still not available in the United States. The lag in the availability of sodium valproate in particular, and the lag and absence of other drugs have substantially reduced the treatment options available to epileptic patients in the United States.

Sodium valproate (Depakene) was first approved in 1967 in France. It was also approved and received phenomenal acceptance in over forty foreign countries before it was finally approved in the United States on February 28, 1978, 11 years after its approval in France. It is regarded as the greateset advance in the treatment of epilepsy in 40 years. Yet FDA classifies it as only a modest therapeutic gain (B) for the treatment of absence seizures including petit mal.

Sodium valproate is also an example of an approved indication lag. Clinically the drug is highly efficacious in the treatment of absence and generalized tonic-clonic seizures. Moreover, it is the most effective compound for treating myoclonic seizures. Individuals stricken with Unverricht's myoclonus epilepsy have been able to walk again after the administration of valproic acid produced a dramatic clinical effect. The compound also has action against partial seizures. FDA still declines to approve the use of sodium valproate for other than absence seizures.

The toxic side effects of sodium valproate are minimal. Transient nausea at the initiation of treatment rarely requires withdrawal of the drug, and there is no excessive sedation when the drug is given alone. For more than 10 years, valproic acid had no fatal side effects, but recently, after many of hundreds of thousands of patients had been treated, it has been implicated in liver failure. Cause and effect relationships have not been proved. In the case of life-threatening or chronic disabling conditions for which currently available medications are inadequate, a reasonable risk must be tolerated. At most, sodium valproate represents a relatively small risk in comparision to its great usefulness and benefit. It must be remembered that certain consequences of not treating, for example brain damage, can occur with uncontrollable seizures.

The delayed benefits to epileptic patients deprived sodium valproate were detailed by Drs. Penry, Masland, and Farrendelli. Dr. Farrendelli, who chaired the FDA advisory committee on neurological drugs, at the time it considered sodium valproate stated: "the delay in FDA's approval of this drug from October 1977 until February, 1978 resulted in at least a quarter of a million unnecessary seizures being experienced by Americans with epilepsy. Each of those seizures carried with it an immeasurable toll of human suffering which might have been prevented."

Dr. Masland said:

> From an analysis of published data, financial analysts for the Commission for the Control of Epilepsy and Its Consequences (created by Congress) estimated that in the United States valproic acid would prevent one million seizures per year at an annual saving of over $100 million in decreased disability and increased earning capacity.

Carbamazepine (Tegretol) Experience with this anticonvulsant drug provides some additional insights into the drug lag. This drug was marketed in the United Kingdom in 1964 and initially tested as an anticonvulsant drug in the United States. It was subsequently found to be valuable for the relief of intractable facial pain (trigeminal neuralgia). When data from the clinical trials were reviewed, reports were received of fatal cases of blood disorders and hepatitis in persons receiving the drug. As a result, carbamazepine was declared too hazardous for use as an anticonvulsant, especially since other drugs were available. However, it was approved for the relief of facial pain since there was no alternative treatment.

However, carbamazepine's use as an anticonvulsant increased in other countries. The hazards proved less than anticipated—the benefits considerably greater. It is an effective drug for the treatment of

complex partial seizures, one of the most difficult forms of epilepsy to control. Additional trials were carried out in the United States and it was approved as an anticonvulsant in 1974—10 years after its acceptance for that purpose in the United Kingdom.

Clonazepam (Clonopin) was introduced in the United Kingdom in 1974 and approved in the United States in 1975. But an intravenous preparation of this drug, used for arrest of status epilepticus, is not marketed in the United States. (Status epilepticus is a form of epilepsy in which continuous seizures may cause death.)

Four other drugs became available in the United Kingdom between 1962 and 1966. These drugs which follow are not available in the United States and they do not appear even to have a sponsoring company: *Nitrazepam* (may be useful in a small number of patients for whom it is a better drug than the presently available clonazepam); *Chlormethiazole; Pheneturide;* and *Sulthiamine* (has limited value but experienced clinicians in the United Kingdom find an occasional patient, unresponsive to other medication, for whom this drug is beneficial).

These cases document that, at least with respect to anticonvulsant drugs, the policies of the United States are more conservative than are those of many other countries. They suggest that this conservatism has delayed the introduction of most new drugs since 1962. The cost and effort involved in achieving approval is probably at least partly responsible for the unavailability of the four other anticonvulsants with limited market in the United States.

(*b*) *Antidepressant drugs*

There are many effective antidepressants which are available in Britain but not in the United States. Some of these drugs, such as *viloxazine*, have important advantages over other drugs in terms of safety, and some drugs, like *mianserin*, have fewer or significantly different side effects.

(*c*) *Drugs for migraine*

Patients who suffer from migraine are also among those who could benefit from the drugs either available exclusively or approved earlier in Britain for that indication—for example, *clonidine*, *propranolol*, and *pizotifen*.

3. RESPIRATORY DISEASES

(*a*) *Antiasthmatic drugs*

The delays in the availability of a number of agents represented severe disadvantages to many asthma sufferers in this country.

(i) *Beta-agonists.*—The beta-agonist bronchodilators orciprenaline (metaproterenol; Alupent), salbutamol (albuterol; Ventolin), and terbutaline (Bricanyl) differ in several ways from the prototype of their series, isoproterenol. They are more reliably absorbed by mouth; they have a longer duration of action; and, most important they are relatively bronchoselective; that is, all three produce less cardiac stimulation for a given bronchodilator effect than does isoproterenol. Salbutamol is the most bronchoselective and orciprenaline the least of the three.

Metaproterenol (Alupent) was approved in the United Kingdom in 1962.

Salbutamol (Albuterol; Ventolin) was approved in the United Kingdom in 1969. It is available in virtually every country in the world except the United States. According to the FDA this bronchodilator drug has been investigated under two IND's: one for an aerosol form submitted in 1969 and one for an oral dosage form submitted in 1970. Because of problems with the metered dose delivery systems, studies of the aerosol were curtailed in 1972, and an NDA submitted (in 1973) for this form was withdrawn in 1974. Similar adrenergic stimulant bronchodilators are available, including metaproterenol, terbutaline and isoproterenol, though albuterol is claimed to be more bronchoselective and to have lesser cardiovascular side-effects. FDA's Pulmonary-Allergy Advisory Committee found that there was insufficient evidence to confirm this claimed advantage in its meeting on November 14–15, 1977. Clinical studies are presently in hold until matters related to possible oncogenic properties are resolved. The NDA was withdrawn from pending status by the applicant on December 16, 1977.

Terbutaline (Bricanyl) was approved in the United Kingdom in 1971 and the United States in March 1974. FDA classifies it as a modest therapeutic gain (B) as a bronchodilator for bronchial asthma and reversible bronchospasm associated with bronchitis and emphysema.

(ii) *Other Drugs.—Cromolyn sodium* (Intal) is the first of a unique class of antiasthmatic agents that prevent the release of biological substances which are mediators of allergic reactions. It has a definite role in treatment to prevent asthmatic attacks. It was approved in the United Kingdom in 1968 but not in the United States until the early 1970s making the United States the 65th country to approve this drug.

Beclomethazone (Vanceril Inhaler) is a drug used for the treatment of chronic asthma and introduced in the United Kingdom in 1967. The GAO found NDA was submitted to FDA in February 1974 and approved in May 1976 or 27 months later. This drug was available earlier in Norway, Sweden, Switzerland and the United Kingdom, and was approved in a much shorter period of time in all four countries. The approval times ranged from 4 months in the United Kingdom to 18 months in Sweden.

4. GASTROINTESTINAL DISEASES

(*a*) *Antiulcer drugs*

Cimetidine (Tagamet) offers a most significant new approach to ulcer therapy by inhibiting gastric acid secretion. Even though the FDA put it on a fast track for approval it was not available until nine months after it was approved in the United Kingdom. The GAO found an application for cimetidine, used to treat duodenal ulcers was submitted to FDA in July 1976 and two months later the application was submitted to the United Kingdom. This drug was approved by the United Kingdom in November 1976 but not by the FDA until August 1977.

Carbenoxolone was introduced in the United Kingdom in 1962 as a treatment of peptic ulcer. According to the FDA two IND's were submitted: one in 1965 for study of its effectiveness in the healing of gastric ulcer, and another in 1972 for study of its effect on the healing

of duodenal ulcer. The sponsor filed an NDA in July 1977. It was considered not approvable in August 1978 because studies in the United States and Canada did not provide substantial evidence that the drug is more effective than placebo. In addition, the FDA says the drug provides certain serious adverse effects (aldosterone like side effects).

(*b*) *Other drugs*

Several other drugs, including the following, have been significantly delayed or are not yet available in the United States.

Metoclopramide (Reglan) was approved in the United States in February 1979. FDA classifies it as a modest therapeutic advance as a gastric smooth muscle stimulant.

Lactulose (Cephuloc) was introduced in the United Kingdom in 1969 and approved in the United States in March 1976. (It represents a moderate therapeutic gain (B).) In another case FDA classifies it as C.

Pentagastrin (Peptavlon) a diagnostic agent to evaluate gastric acid secretory function was approved in the United States in July 1974. FDA classified it as a modest therapeutic gain (B).

Chenodeoxycholic acid, is a drug which was approved in 1976 in Switzerland and is used to dissolve cholesterol gall stones, thus avoiding the necessity for surgery in some patients. It is not approved in the United States. According to the FDA, chenodeoxycholic acid is the subject of many IND's, the most important of which was submitted for the National Collaborative Gallstone Study (NCGS). This study is funded by the NIAMDD, and it is intended to examine, in a well-controlled way the long-term safety and effectiveness of the drug. The NCGS began in 1975 and is expected to be completed in 1980.

5. CANCER TREATMENT

In this area, the issue of patient safety versus risk entailed in aggressive pharmacologic intervention when related to the consequence of the disease has spurred considerable controversy and debate within and between the medical, scientific, pharmacological and regulatory community. For example, intravenous *allopurinol* is a needed palliative agent to treat high blood urate levels in cancer patients who can not take the currently available drug by mouth. It has been delayed more than seven years and is still not available according to Dr. Regelson. One reason for the delay was "the high incidence of death associated with its use". Cancer patients who cannot take drugs by mouth are severely ill and a special category of patient.

Adriamycin is an example of the delays in availability of anticancer therapeutic agents in the United States. The United States was the 32nd country in the world to approve this important anticancer drug.

In the cancer area an important issue is difficulties encountered in conducting rigorously controlled clinical trials with promising agents. One of the major centers of debate is whether one should treat anticancer drugs with the same strictness as one evaluates common cold nostrums.

In relation to the above, should carcinogenesis, as a side effect of a drug, be of major concern at this stage of our understanding of cancer treatment and/or in a patient with myocardial infarction, if prognosis is limited to days or months of survival? The inability to make

distinctions among medical and regulatory priorities may have unnecessarily delayed clinical trials of several promising anti-cancer immune stimulants below:

Thymosin: The FDA demanded the same animal toxicology data for its synthesized purified degradation product as for the cruder preparation already in clinical testing. It is apparent that biological degradation will produce this product when the crude preparation is metabclized. These drugs are designed to treat patients with severe immunodeficiency disease and/or advanced cancer. Should the FDA have been that strigent in having to provide animal guidelines for toxicology when it would appear more important the drug be released for clinical testing in patients whose prognosis is obviously poor? It needs to be recognized also that animals differ from man in toxicology and immune response.

Levamisole: The FDA will not accept historic controls for this anti-cancer immunoadjuvant or non-double masked studies despite data that are accepted by others in cancer patients with limited prognosis. Who is there to consider an appeal of the FDA decision? Can there be a prioritization of disease categories in relation to patient prognosis? It would be rather strong to call levamisole a "breakthrough". The priority system for disease categories could avoid this ambiguity. This becomes even more pertinent with better immunomodulators such as thymosin or interferon.

Furthermore levamisole has been awaiting approval for its use as an anti-helminthic (vermifuge) for two-three years. According to Dr. Regelson, this approval will be held up indefinitely because someone in the FDA says "the drug will be used to treat cancer patients under the guise of treating worm infestations". He has challenged the drug company involved to "sue the FDA if they don't like his decision".

Companies are afraid to take on such issues and will not sue because of fear of FDA punitive action against them in other areas. There is a need for an appropriate appeals structure in which the FDA is not both judge and jury.

Cinanserin is a cinnamic acid derivative which had potential anti-tumor activity. It was an excellent immunosuppressant which had some clinical value in rheumatoid arthritis. The FDA ruled that the drug was not to be used above a certain dosage because it produced some "damage to the liver" as measured by a liver enzyme increase (SGOT) despite reversibility. This restricted the drug to a fixed dose threshold and made it impossible to appropriately use it in the treatment of rheumatoid arthritis. Additionally, it was found to cause cancer in the liver of rats. However, Dr. Regelson demonstrated it having a striking value in the treatment of a lupus-like syndrome and was able to maintain a patient at home on this agent who was otherwise totally crippled with joint inflammation and progressive renal damage. When the observation was made that the drug caused cancer in rats, Squibb, because of fear and insecurity, in relation to FDA rulings, stopped making the drug available. The patient then went back on her corticosteroid (prednisone) maintenance, relapsed and perforated a steroid caused gastric ulcer. The drug was given up because of FDA fears and limitations that would have similarly prevented prednisone from reaching the market. There was no appeal system to keep this drug alive.

6. DRUGS FOR OTHER DISEASES

A number of other drugs could have made significant improvements in therapeutics if they had been available earlier in the U.S.

Bromocryptine (Parlodel) was approved almost 3 years earlier in Switzerland than its approval in the United States in June 1978. It was approved in the United Kingdom in 1976. Bromocryptine is used to treat an endocrine disorder of the uterus and breast (prolactin inhibition), Parkinson's disease (a nervous system disease common in older people), and acormegaly (an endocrine system disease with a particular affect on the bones). FDA classifies it as an important therapeutic gain for the temporary relief of amenorrhea and galactorrhea.

Cyproterone, was approved 6 years ago in Germany and is used in the treatment of sexual hyperactivity and precocious puberty. It is not approved in the United States.

According to the FDA cyproterone acetate is a potent progestational agent of potential significance being investigated for various indications including benign prostatic hypertrophy, sexual hyperactivity, sexual deviance, and central nervous system effects. IND's were submitted by five sponsors during 1968, 1973, 1974. Clinical trials are currently in progress in phases I and II, with the major research being conducted by individual investigators under research IND's. An alternative progestin available in the United States for the endocrinologic indications only is medroxyprogesterone acetate (Depo-Provera). Cyproterone has been used abroad as an anti-androgen for sexual offenders. Two IND's for this use were submitted by individual research investigators in 1973. A drug useful in the treatment of sexual criminals would be an important therapeutic advance, but major questions of safety and efficacy for this use remain to be clarified according to FDA.

Somatotropin (Asellacrin) is a drug FDA classified as important (A). This drug, which is used to promote growth in children with short stature due to a deficiency of pituitary growth hormone, was approved on July 30, 1976, about 15 months after an NDA was submitted to FDA. Somatotropin was approved for use in Sweden in 1971 and in the United Kingdom and Switzerland in 1972.

Bretylium tosylate is an adrenergic blocker.

Bupivacaine hydrochloride (Marcaine) is a longer-acting local anesthetic agent licensed by Sterling Drug from a Swedish firm. That agent had been marketed in Europe at least since 1967, in the United Kingdom since 1968. After extensive clinical trials sponsored by us in the United States, an NDA was filed with FDA in August, 1970; approval was granted in October, 1972 (26 months later).

Levodopa is an anti-Parkinson agent.

Baclofen (Lioresal), a muscle relaxant was introduced in the United Kingdom in 1972 and approved in the United States in October 1977. It represents a modest therapeutic gain (B) according to FDA.

Danazol (Danocrine) is a gonadotropin. An NDA was filed with the FDA on December 18, 1973 for use in endometriosis, a clinical disorder of women for which no satisfactory medical treatment previously existed. Approval was received on June 21, 1976, a little more

than 30 months later. A submission was made in the United Kingdom on December 27, 1973 and the Republic of Ireland on January 23, 1974. The non-domestic submissions contained only data obtained from studies in the United States, the same data submitted to the FDA. Approval was granted in the United Kingdom on June 6, 1974 (a few days longer than 6 months after submission); approval was granted in Ireland on May 24, 1974 (4 months after submission).

A supplemental application was filed with the FDA on March 6, 1978 for an additional indication, fibrocystic breast disease, already approved in the United Kingdom and Ireland. Action on this submission was still pending at the FDA 16 months later.

Desmopressin (DDAVP), an antidiuretic (B), as introduced in the United Kingdom in 1975 but not approved in the United States until 1978.

Calcitonin is a blood calcium regulator.

Dimethyl sulfoxide (DMSO) can be derived from lignin, the cement substances of trees or can be made from a number of organic chemicals. Although the chemical history of DMSO goes back to 1866, promise of this chemical in the medical sciences was shown in 1959 with the demonstration of its protective effective on red blood cells and other tissues from freezing damage and later with its ability to serve as a "carrier" drug in conveying other substances through the skin and mucous membranes.

In early clinical studies, dimethyl sulfoxide was shown to relieve pain, reduce swelling, slow the growth of bacteria, improve blood supply, soften scar tissue, enhance the effectiveness of other pharmacologic agents, serve as a diuretic, and act as a muscle relaxant.

The first report on the use of dimethyl sulfoxide as a pharmacologic agent was writen in 1963 and published February 1, 1964. The first IND to study DMSO clinically in the United States was submitted on October 25, 1963. Three NDA's on DMSO were submitted to the FDA in 1965. All were turned down. A fourth NDA was submitted in 1970. It was also turned down by the FDA, in spite of mounting evidence in the scientific and medical literature of the potential pharmacological importance of DMSO.

According to Stanley Jacob:

> Of major importance is the fact that DMSO has been shown to be of value, not only in diseases for which there is other known treatment, but in a number of illnesses for which no other effective or low risk treatment is known, such as the painful ulcers of the fingers in patients with scleroderma....
>
> The value of DMSO in other illnesses for which effective pharmacologic treatment does not presently exist, includes severe abacterial prostatitis, Dupuytren's contracture, subcutaneous scarring from cobalt irradiation, keloids, Peyronie's disease and potentially in otherwise "irreversible" injury to the brain and spinal cord. . . .
>
> Dimethyl sulfoxide is a useful adjunct in the treatment of rheumatoid arthritis, degenerative arthritis and gouty arthritis. It primarily will relieve pain, but will also reduce inflammation and increase joint mobility. Due to its effec-

tiveness in the treatment of arthritis, Americans by the thousands are flocking to nations such as Mexico to receive DMSO. . . .

The effectiveness of DMSO has been demonstrated by comparative studies, by "double blind" studies, and by the clinical impression type of evaluations in man. . . . (and)

A broader spectrum of primary pharmacology and clinical benefit, both actual and potential, has been described in the scientific literature for DMSO than for any other substance with which I am familiar.

In spite of the mounting evidence of the clinical importance of DMSO, it is only prescriptive in the U.S. for interstitial, evstitis (humans) and for acute musculoskeletal problems in large and small animals. DMSO is prescriptive in Canada for scleroderma, in Great Britain and Ireland for shingles when mixed with IDU, and in Germany, Austria and Switzerland for a range of disorders for topical administration. It is also widely prescriptive in South America and has been prescriptive in the U.S.S.R. since 1971. An NDA submitted to the FDA in 1977 on DMSO for scleroderma is currently in an administrative limbo.

In spite of much scientific literature to the contrary, FDA continues to indicate that there is insufficient toxicological information available on DMSO and that the definitive double-masked study on this drug has yet to be done.

Dinoprostone (Prostin E 2), a prostaglandin was introduced in the United Kingdom in 1972. It is used for elective abortion, evacuation of uterine contents in fetal death and the management of benign hydratidiform mole. FDA classifies the drug as a modest therapeutic advance (B) and did not approve it in the United States until August 1977.

Medroxyprogesterone acetate (Depo-Provera), an injectable contraceptive agent, has been approved in many countries around the world. Its NDA for that use has been under consideration by the FDA for over 12 years (since Feb. 1967). Depo-Provera has now been marketed for contraception in over 60 countries and has been used safely for over 6 million woman-years. But on March 7, 1978 FDA ruled it was non approvable in the United States. The reasons why FDA has not approved Depo-Provera have been the subject of another series of congressional hearings conducted by the Select Committee on Population. ("The Depo-Provera Debate", hearings before the Select Committee on Population, U.S. House of Representatives, 95th Congress, second session, August 8, 9, and 10, 1978, U.S. Government Printing Office, Washington: 1978).

Depo-Provera represents an approved indication lag. In 1972, FDA approved this drug for adjunctive therapy and ralliative treatment of certain types of inoperable cancer of the uterus.

Metrizamide (Amipaque) is a breakthrough radiodiagnostic agent licensed by Sterling Drug from a Norwegian firm. An NDA was filed with the FDA on December 27, 1976; approval was granted on August 22, 1978 (20 months later). That agent had been marketed in Scandinavian countries since 1974 and was approved for marketing in the United Kingdom in April 1977 (it is marketed there by the

Norwegian firm). In France, Sterling made a submission on August 22, 1977 and received approval in February 2, 1978 (5½ months later).

Rifampin is an antituberculosis drug.

Trimethoprim is an antibacterial agent.

Vidarabine (VIRA–A) an antiviral, was approved by the FDA in November 1976 but only as an ophthalmic ointment. It is classified as an important therapeutic gain (A) for the treatment of herpes keratoconjunctivitis.

The subcommittee finds that the numerous examples of important or significant drugs which have been delayed and in some cases not yet approved leave no doubt that U.S. patients have suffered a number of significant therapeutic losses. FDA appears to raise safety issues on many drugs which have been in use for years in advanced countries without any problems. These are countries which also are reported to have good post-marketing surveillance programs in operation.

One is lead to the realization that, if the most up to date advances are not available in the United States, there will be a therapeutic deficiency relative to other advanced countries which have these therapies. It follows that some patients denied this benefit will die or suffer unnecessarily. This automatically results in a diminution in the quality of life and the health care of those who are ill.

The United States prescription drug laws were designed to protect citizens by preventing general public access to new drugs which could result in harm to the recipient, if unsupervised. It must be remembered that all drugs have serious potential side effects and all drugs are capable of serious harm if misused or abused. Therefore, safety is relative and both patients and regulators must assume some risk. Levels of public expectations and regulatory goals must be modified to appreciate the necessary balancing of benefits and risks in advancing new and effective drug therapies.

D. The Need for a Variety of Drugs

Although many disease areas have numerous drugs available for their treatment, the subcommittee recognized the need for a variety of drugs for optimum treatment. Drugs not being available simply reduce a physician's and patient's option for the most beneficial treatment for the illness. Discussing sodium valproate, Dr. Farrendelli stated:

> Even with the 15 anticonvulsants available in the United States at this time, only about 50 percent of epilepsy patients could achieve complete control of their seizures. Another 30 percent could achieve partial control and the remaining 20 percent little or no control. More drugs are needed to control seizures in the 50 percent of the epilepsy population for whom presently available therapy doses not provide complete control.

Dr. Zipes summed it up as follows:

> It is as naive to think that one antiarrhythmic drug will be effective for patients, as it is to think that one antibiotic will cure all infections. Therefore, physicians need to be able to choose from a wide selection of antiarrhythmic agents that

have widely different electrophysiologic properties. No ideal universally effective antiarrythmic agent exists. If it did, such questions as to whom to treat and with what drug would not occur. Different causes of an arryhthmia may allow a drug to be effective in one patient but not in another.

Virtually all the available antiarrhythmic agents have significant side effects that may vary from patient to patient. One may produce crippling diarrhea in one patient, and be tolerated without any problems in another. Clinicians must continue to evaluate the benefit-to-risk ratio of any drug and be able to select an effective drug that does not produce side effects for any given patient. To do this, there must be a wide spectrum from which to choose.

Few if any drugs are effective in all patients. In fact, most drugs are effective in only 30 to 75 percent of the patients. Even seemingly unimportant drugs may help a few people and for those few people they are very important.

The subcommittee concludes that the U.S. drug lag has an adverse impact on medical treatment and hence health care in the United States.

III. FACTORS CONTRIBUTING TO THE "DRUG LAG"

The fact that there is a delay in the marketing of a drug does not always mean that FDA is responsible. The subcommittee found a number of reasons why a drug can be delayed in its availability to patients in the United States compared to other technically advanced countries. These factors can be attributed to the FDA, the sponsor of an NDA and/or the discoverer of a new agent if the discoverer is different from the sponsor. FDA related factors appear, however, to be the primary reason for delays.

A. FDA Related Factors

1. SLOWER FDA ACTION TO APPROVE NDA'S

This is a major factor contributing to the delay in the approval of most drugs. The GAO found that most technically advanced European countries have approval processes that are 7 to 12 months shorter than the 20 month average the GAO found in the United States. The GAO's determination of 20 months is low because it is based on the approval of 68 of 132 NDAs filed with FDA in the calendar year 1975 and approved as of June 30, 1978. As some of the remaining 64 NDAs are approved, this 20 month average will increase. FDA's own analysis for 80 NDAs approved in fiscal 1978 was 34 months. This may be a more accurate time frame to consider for all NDA's. The only countries that the GAO found to have comparable approval times were Sweden and Norway. Approval time in Sweden was 27 months and Norway was (1 to 3 years). This leads to the conclusion that FDAs drug approval process is longer than that of most technically advanced countries. Clinical researchers and industry representatives support this and add that the clinical research stage during the IND phase is also longer in the United States.

2. MORE CUMBERSOME U.S. REGULATIONS FOR CLINICAL TESTING

Agency responsibility for the delay of a new drug can involve both the approval stage and the clinical research stage of development. A long approval time in one country could be offset by a more expeditious clinical research stage or *vice versa*. Or a long clinical research stage coupled with a long approval stage would result in even greater delays. The latter is generally the case in the United States.

The initiation of clinical studies in the United States is more cumbersome and has more FDA involvement than similar studies in other technically advanced countries. This is of course due to FDA's great concern for the protection of human rights in the conduct of clinical investigations. In the United States the FDA determines initially whether a clinical trial can begin. First, a claimed exemption for an Investigational New Drug (IND) must be filed by the sponsor. If

FDA does not reject the IND or request further information, the sponsor can begin studies in 30 days provided these studies have also been approved by the institutional review board (IRB) of the institution in which the clinical studies will be conducted.

In other technically advanced countries, there is less agency involvement and the sponsor deals directly with the institution and the investigators who will conduct the clinical research. The result is that clinical studies can often be started earlier in other countries. More flexibility is also permitted in foreign studies. In the United States the sponsor must spell out in considerable detail a definite clinical protocol (plan) to be followed. By establishing a well-defined clinical plan in advance of the clinical trial, it is hoped that this plan can be followed exactly throughout the course of the clinical study. By its nature, however, research, including clinical research, often does not proceed exactly as planned. Changes in protocols are frequently required. In the U.S., all changes must be approved by the FDA. This can result in further delays.

The exact progression from Phase I to Phase II and then Phase III studies is spelled out by FDA with a number of check points and requirements for the sponsor to report to the FDA. The overall result of the frequency of reporting requirements is that clinical studies take considerably longer to complete in the U.S. compared to other advanced countries.

One of the most profound changes in the U.S. since the early 1960's is the drug study (IND) period. For example Upjohn representatives testified that:

> The IND period was about 36 months (3 years) on the first several Upjohn candidates studied entirely under the 1962 Kefauver-Harris drug regulations. NDAs on five NCEs (New Chemical Entities) submitted to FDA by Upjohn during the past 24 months show IND times ranging from 71 to 123 months (6–10 years), with an average of 102 months (over 8.5 years).

Mr. Hoff, attributes these increases to "the buildup of government regulation and a growth in the amount of data which can be gathered on drug safety and efficacy, that is improvements in the "state of the art."

Good clinical practice regulations are making the clinical research stage more cumbersome and also more expensive to the pharmaceutical companies, the clinical research institutions, the government, and, ultimately, the public. These clinical regulations are probably also contributing to delays as well.

3. FDA REGULATIONS AND REQUIREMENTS MAY LENGTHEN THE PRECLINICAL TESTING STAGE

This is an area of growing concern to those concerned about the "drug lag". The most notable example of a delay involves the beta-blocking drugs. Clinical testing of the whole series of beta-blocking drugs was substantially delayed because FDA required extensive animal toxicology (carcinogenicity testing) before allowing long term human trials to be conducted. In other cases FDA has required further

animal testing even after substantial human experience in Europe had not revealed any problem.

Recent FDA good laboratory practice regulations have made the preclinical research stage more cumbersome and expensive and may cause be a contributing factor in some delays. The components of the increased preclinical workload are shown through increased size of the INDs.

The subcommittee finds that FDA's longer drug approval process and more cumbersome regulations for clinical testing of drugs are major factors contributing to the delay in the availability of new drugs to American patients.

B. Sponsor Related Factors

1. ECONOMIC POTENTIAL OF THE DRUG

(a) Development costs versus profits

With research and development costing $30 to $50 million for a pioneer new drug, a prime requirement sponsors consider is whether profits from sales of that drug will repay the investment. This becomes a particular problem with drugs for "orphan diseases"—diseases which affect 100,000 or fewer people in the U.S. In these cases the expense of clinical research and regulatory requirements become high relative to anticipated profits. In such cases the development of these drugs often proceeds on a lower priority basis. This problem is accentuated in the United States because the FDA requires that clinical studies be done in this country regardless of the number or quality of clinical studies conducted abroad. Development of mechanisms whereby FDA would evaluate and accept well controlled foreign clinical trials in the place of domestic trial would considerably ease "orphan diseases" drug development costs.

Industry decisions to market a drug are not always based on the size of the market. For example, Abbott Labs did decide to market sodium valproate for epilepsy and Upjohn has developed Prostaglandin in E_1, which is used to treat infants born with congenital heart defects. This lifesaving drug is being developed by Upjohn as a public service with the hope that other important applications might ultimately be developed. In this case development costs, and even production, marketing, and distribution costs, may never be recovered. In general, industry cannot be expected to develop large numbers of drugs under these circumstances.

Acceptance of foreign clinical data in lieu of domestic studies, and the development of a "compassionate NDA" would be two means of encouraging the development of drugs for "orphan diseases." A "compassionate NDA" would be a mechanism whereby a promising drug could be marketed early with the patients then serving as a basis to establish the evidence needed for well controlled trials that is needed for Phase III. It is essential to reduce the testing timeframe and hence the costs to promote the development of these drugs.

(b) Patent rights and licensing problems

Because of the high development costs a sponsor is not likely to develop a drug in the U.S. unless it is protected by a patent which will still have a reasonable life after the drug is approved. The shorter the

patent life after approval the less interested a sponsor is likely to be in developing a drug.

Often when one patent holder does not have the resources—economic or expertise—to market a drug, patents are sold or rights are licensed to another sponsor. This takes time to accomplish. Again this is true patricularly for drugs that do not have a large market such as sodium valproate. The original patentee of sodium valproate was the French company Labaz. Although marketed in France in 1967, evidently Labaz was not interested in or able to market the drug in the United States. It was not until late 1974 that an American company (Abbott Laboratories) completed agreements to market sodium valproate in the United States.

Although factors like licensing problems were a significant factor in the review and approval lag of sodium valproate, similar factors do not appear to be as important in review and approval delays experienced with other drugs.

(*c*) *Lower costs of foreign clinical studies*

Over the past decade the lower costs of foreign studies as well as greater ease in initiating studies abroad have caused many large U.S. pharmaceutical companies to do some of their clinical research abroad. It is natural that studies started first abroad will be finished first abroad with drugs being approved there as well. Foreign companies on the other hand seldom (if ever) begin their studies first in the United States.

2. TECHNICAL PROBLEMS

Technical problems do occur from time-to-time and cause the sponsor to take time to improve the drug product. Again sodium valproate was marketed in Europe as valproic acid, a somewhat unstable form, and the U.S. sponsor chose to take time to develop a better formulation, sodium valproate.

3. INDUSTRY PROCESSING TIME

The GAO found that part of the time to approve NDAs is due to FDA waiting for industry's responses to FDA inquiries. This may relate to the priority that industry places on the development of a particular drug. This phenomena is most likely not unique to the U.S. pharmaceutical industry. Still average foreign approval times are shorter than in the U.S.

4. ABANDONMENT OF ONE DRUG IN FAVOR OF ANOTHER

An example illustrating this is the anticonvulsant drug nitrazepam. Although approved in Europe as a sedative, the sponsor terminated their clinical investigations in favor of a superior agent, clonazepam (see II.2.a). Some investigators think nitrazepam could have advantages for a small number of epileptic patients. Nitrazepam is now an orphan drug for epilepsy. No further efforts will likely be made to market nitrazepam in the United States because of costs and the fact that clonazepam is more effective for a large patient group.

5. TECHNOLOGY TRANSFER OF MEDICAL INFORMATION

In the sophisticated era of electronics and computers, it seems difficult to imagine that this could be a problem. Again sodium valproate is an example. Although approved in France in 1967 there does not appear to have been any real U.S. interest aroused regarding the significance of this drug until 1970.

The sponsor related factors do not appear to show a consistent pattern in delaying the drug development and approval process. An exception is the case of drugs for orphan diseases. With drugs for orphan diseases sponsor related economic factors, patent and licensing problems, abandonment of a drug and technology transfer of medical information can be more significant than FDA related factors.

Initiation of clinical trials overseas appears to be a more general sponsor related factor but this also relates to a slower and more cumbersome FDA process in this country. Also industry processing time should not differ significantly compared to foreign countries unless it is also FDA related. Therefore, the slower FDA approval processes are the most consistent factor in the delay of new drugs.

The subcommittee concludes FDA's regulatory requirements and slower procedures are the major factors contributing to the drug lag in the United States.

IV. REASONS FOR FDA'S SLOWER DRUG APPROVAL PROCESS

The total drug development and approval process in the United States is slower because of more extensive regulatory requirements for animal testing and human trials (Phases I, II, and III) as well as FDA's slow review process. FDA portrays an attitude of distrust of industry (sponsors) and clinical researchers. FDA's overall attitude is adversarial in contrast to more cooperative government-industry attitudes in technically advanced countries in Europe. Yet, as discussed previously, there is no evidence, in spite of FDA's claim of providing the highest standards in the world, that Americans today are being guaranteed safer and more effective new drugs. The Subcommittee's more specific findings are discussed below. A number of these are administrative problems which FDA appears to be trying to correct. Others related to regulations and policy will likely require longer term attention and possibly legislation.

A. Internal or Management Problems at FDA

There have been numerous charges of FDA's lack of effective management techniques exemplified by the problem discussed below. Internal management problems are difficult to solve by legislation, although S. 1075 includes time limits to try to encourage better management practices. FDA is presently trying to solve a number of these problems. In the future more scrutiny of FDA by FDA itself and through Congressional oversight are needed to follow up on internal problems.

1. FDA COMMUNICATIONS WITH INDUSTRY ARE SLOW

Slow or inadequate communications from the FDA have contributed to delays in reviewing and approving drugs. Some companies consider this to be the prime reason for delays because FDA does not provide timely feedback regarding deficiencies in an NDA. GAO finds that FDA reviewers corroborated these perceptions and that correspondence between FDA and industry on NDA deficiencies regarding chemistry and manufacturing control in some cases have continued for a year or more. Industry thinks that the FDA's formalized rules discourage good communication.

2. SCIENTIFIC AND PROFESSIONAL DISAGREEMENTS BETWEEN INDUSTRY AND FDA ARE NOT READILY RESOLVED

There is presently no effective formal mechanism for the resolution of scientific disagreements which arise between a drug sponsor and the FDA. Drug sponsors can request an administrative hearing to resolve such issues but the procedure is time consuming and used infrequently.

Unless drug sponsors can persuade FDA to change its position the sponsors have little choice but to do what FDA wants. Otherwise there is little chance the drug will be approved.

These disputes range from manufacturing controls to toxicology and clinical research problems. For example, Dr. Wesco reported upon a significant delay related to Sterling Drug's IND for rosoxacin, an antibacterial that showed remarkable activity in the laboratory against the gonococcus.

> In November, 1976 we filed a protocol with the FDA for a trial in gonorrhea while another clinical trial of this agent in urinary tract infections was in progress. FDA denied us the right to begin the trial because of an ostensible problem with crystalluria. In our opinion it was unscientific to delay a one-day trial in gonorrhea when a multiple dose study for 14 days was permitted in urinary test infections. Even after the ostensible problem was resolved, the FDA delayed another 8 months in permitting us to begin the trials in gonorrhea. That approval was granted in March, 1979. In the interim, beginning in late 1977 we began sequentially, on the basis of U.S. data, to proceed with clinical trials in gonorrhea in other countries. With little delay, studies were initiated in the Philippines, Holland, Colombia, Germany, Austria, Belgium and Finland. In fact, rosoxacin will probably be marketed in one or more of these countries before the NDA is filed in the United States.

Sterling's experience has been that regulatory agencies outside our country act expeditiously in the large part even when data are derived from studies in the U.S. Scientific differences are resolved in a scientific manner. In those countries, the relationships between industry and the regulatory agencies are not adversarial. Despite FDA's contention that most scientific and related disagreements with industry are resolved quickly, the subcommittee finds there is opportunity for considerable improvement in this area at FDA. The subcommittee finds that various solutions could be used toward resolving scientific disputes, such as to submit the dispute to the FDA advisory committee, a panel of the National Academy of Sciences, or other independent boards of experts from medical institutions for resolution.

In development of a more formal appeals system for resolving scientific disputes between industry and the FDA, considerable consideration should be given by the FDA to establishing an ombudsman capability within its organization. This Office of the Ombudsman should be of high level within the FDA and would promote and track the progress of all aspects of the drug review and approval process and would maintain good and open communications with industry, consumer protection, and medical groups. The Office of Ombudsman would also be responsible for being current regarding drug advances and developments both domestically and internationally and would serve in an advocacy position within FDA for encouraging early testing and introduction of significant new therapeutic advances in the U.S., to identify and bring to the attention of the Administration and Congress barriers to such, and to encourage policies and for legislation to facilitate FDA's drug review and approval process.

Pending drug regulatory reform legislation also recognizes the needs to establish procedures for the expeditious review and resolution of scientific disputes between industry and the FDA.

3. MANAGEMENT OF HUMAN RESOURCES NEEDS IMPROVEMENT

(a) FDA reviewer changes during NDA review

GAO found that in a 45 case sample, reviewers changed once in 38 percent of the cases and more than once in 11 percent of the cases. This presents an enormous problem to industry because the subsequent examiner essentially started the review over, re-examining all the data that had been previously reviewed. The magnitude of this is realized when one considers that an NDA which often consist of hundreds of volumes (100,000 pages or more) are usually reviewed by 3 to 5 people. Changes of reviewers are unavoidable if an individual leaves the agency but in other cases changes need to be avoided.

(b) Uneven workload of reviewers

Workload is unevenly distributed among FDA reviewers. The GAO found that 50 percent of the FDA reviewers were responsible for reviewing substantially more than 50 percent of the NDAs. Some of this is obviously attributable to differences in reviewers' abilities. With a relatively small force of approximately 160 reviewers, it is more disturbing that they spend less than 20 percent of their time reviewing NDAs and less than 10 percent of their time reviewing supplemental NDAs. An exception is chemists who spent 27 percent of their time on supplemental NDAs. The bulk of reviewers' time is apparently spent on reviewing INDs, attending professional training courses, and handling congressional and freedom of information requests.

The amount of work to be reviewed has increased considerably over the past decade. The number of new drug submissions per FDA reviewer has increased from the low twenties in 1971 to the high thirties in 1978. Coupled with this, the number of new drug reviewers over the past decade has been about 160 to 180 and is now near the lower end of that range. Also the amount of data in both INDs and NDAs has been steadily increasing. Workload is an obvious bottleneck in the slow review process. To speed up the action on submissions the FDA has only four alternatives:

Increase the number of reviewers;

Have reviewers spend more time reviewing submissions;

Decrease the requirements for data to be reviewed (e.g. expert summaries of the data rather than all raw data); and/or

Increase the efficiency of existing personnel and the review process by using better management techniques.

(c) Quality of personnel

FDA has trouble keeping good personnel. This problem has also been a finding of other investigations. For political reasons the agency appears to have less freedom to promote and encourage scientific progress among some of their key employees and to move out people who do not do a good job.

Witnesses stated there are people in the lower ranks who appear to be immobile. They have never approved any drug and have immobilized, for example, the cardiovascular area where no pioneer new drugs were approved for a decade.

GAO found that:

> According to an FDA Bureau of Drug official, FDA has no written performance standards for evaluating reviewers; evaluations are based on the subjective judgment of supervisors. FDA has 164 drug reviewers. Of these, 104 are grades GS–14 and below, 50 are GS–15 or above, and 10 are Public Health Service commissioned officers. Reviewers in grades GS–14 and below and Public Health Service commissioned officers are given written performance evaluations annually. Evaluations of other reviewers are not made in writing.

4. FDA COULD MAKE BETTER USE OF COMPUTERIZED INFORMATION SYSTEMS

GAO found that most FDA reviewers did not use and, in fact, were not aware of FDA's automated information systems and what they contain. FDA's computerized information systems also appear to lack the ability to retrieve sophisticated scientific and technical information. Because FDA's computer resources are not adequately used to support FDA reviewers, the subcommittee supports the GAO recommendations that FDA should:

> Evaluate the existing information systems to determine how they can better serve reviewers,
>
> Make a survey of the needs of the reviewers that can be used in developing or redesigning information systems, and
>
> Develop an education program for reviewers in the use of information systems.

5. SLOW REVIEW PROCESS

A major contributor to the slow review process must be the increasing amount of work per reviewer (see section 3b above). Also FDA relies heavily on a formalized process in its review of individual case records instead of accepting study summaries prepared by experts. This coupled with management problems involving communications, scientific disputes and human resources results in the regulatory review process moving at a slow pace.

Changes in statute or regulations will not likely solve managerial shortfall. Effective managerial techniques, an insistence upon the meeting of responsibilities in timely fashion, could lead to an improved, more rapid, more equitable review process. Congress should mandate that the FDA base its procedures and policies on the fact that its primary object is to bring to the American public effective medicines with a reasonable benefit/risk ratio at the earliest time possible.

The subcommittee recommends more scrutiny of FDA by both GAO and congressional oversight to see that these management problems are corrected.

B. Problems With FDA's Regulations and Guidelines

There is a general consensus that FDA has a very high concern for safety, and in fact may be preoccupied with safety when promulgating regulations and guidelines. Consumer activists support this approach while clinical researchers, physicians, drug sponsors, and many pa-

tients do not think this is realistic in the present state of knowledge of drug development and medical treatment. No drug is 100 percent safe under all conditions. The risks versus the benefits of a drug need to be considered. The sick are willing to accept reasonable risks to reap the benefits of a drug. There is no other reasonable choice. They can not make any choice if the drug is not approved. Physicians charged that FDA regulations fail to take into account the overriding responsibility to the dying and severely debilitated.

1. FDA REGULATIONS HAVE BECOME EXTENSIVE AND COMPLEX

The great concern for the safety of test subjects and establishing the safety of the drug under conditions of use have greatly expanded FDA regulations. The amount of data to meet safety and efficacy requirements have expanded enormously in the past two decades. This is due to regulations and to state-of-the-art advances. Regulations in technically advanced countries abroad are less cumbersome without compromising patient safety and drug efficacy. Consequently they allow the clinical research process to move faster.

2. U.S. CLINICAL STUDIES

The FDA's basic requirement for the approval of a new drug is that a sponsor must clinically test the drug under closely controlled conditions. This must include adequate and well controlled studies demonstrating substantial clinical evidence of safety and effectiveness. Well controlled studies must almost always be conducted with the drug compared to placebo and must be marked and double marked. Particular problems with the regulations which contribute to slowing down the process are the following.

(*a*) *Requirements for the protection of human subjects*

The FDA has established very stringent requirements for the protection of human volunteers who participate in clinical trials of new drugs. United States regulatory requirements for animal testing, sponsors and monitors, clinical investigators, institutional review and informed consent are intended to minimize the risk and assure that investigational subjects are fully aware that risks exist. In addition to these protections for all test subjects, the Department of Health and Human Services (HHS) regulations provide special protection for children, pregnant women, the fetus and abortus, prisoners, and mentally infirm used as subjects in research studies. Many clinical researchers have complained about the magnitude of effort needed for compliance but not necessarily the intent of such requirements.

(*b*) *Early Clinical Research (Phases I and II)*

Phase I and Phase II studies are carried out in small numbers of volunteers in order to determine whether the drug merits the more extensive Phase III studies. FDA is extensively involved in these early stages of clinical research. This begins with preclinical requirements in order to meet the requirements of an IND submission. Changes in clinical protocol cannot be made without FDA's consent. The detailed informed consent requirement (discussed above), and other reporting requirements establish checkpoints which slow down

early clinical research in the United States compared to other technically advanced countries.

For example the GAO found:

> The drug regulatory process of the United Kingdom does not regulate the initial testing of new drugs on healthy humans—referred to as Phase I testing in the United States. Because the vast majority of new drugs fail for various reasons, such as lack of bioavailability, during Phase I testing, the exemption from regulation during Phase I permits drug companies to identify viable new drugs in the shortest time and least cost. This exemption also reduces the number of investigational drugs agency reviewers must review and monitor. We are not aware of any problems with human ethics and drug testing resulting from this policy.

Dr. McMahon, a noted clinical researcher, best summarized the situation (including Phase III) by saying:

> Europeans have some common sense that we have lost track of. I think the bioresearch monitoring regulations ought to be reviewed. They have ensnarled research at our institutions terribly and irreversibly, especially the sponsor monitor regulations . . . It's really absurd to sit still and sign your name 400 times on 400 pieces of paper. It is ridiculous to try to explain to a layman investigator from the FDA why you dared to use a patient whose urine specific gravity was 10.08, because the normal in your lab is 10.10 to 10.25. He probably had an extra glass of water that morning that changed it."
>
> You cannot educate FDA inspectors to that minutia. You have to use some commonsense. We have lost sight of common sense. We are ensnarled with regulations and bureaucracy, and we ought to change the direction of the FDA; we ought to turn them around, and to turn them around I would take them away from Phase I and Phase II almost entirely.

The Subcommittee finds that the most useful supervision of early clinical research (Phases I and II) is by the physician and the collaborating institution. It is well recognized by those involved with these studies, including FDA, that they have an excellent safety record.

The subcommittee concludes FDA should become less involved in the early stages of clinical research by streamlining and uncumbering its regulations governing them. Legislation may expedite this change.

(c) *Phase III studies (later clinical research)*

Phase III studies take place in hundreds to thousands of patients in order to prove substantial evidence of efficacy. They almost always require masked and double masked drug versus placebo controlled studies to prove that the drug is effective meeting statistical requirements. Several problems arise.

FDA has inflexible standards for scientific evidence regarding substantial evidence of efficacy. The drug DMSO (see II.6), for example, cannot meet the requirements of masked and double masked studies since, unlike placebo, it causes a garlic-like taste in the mouths of patients who take it. This has been a stumbling block in proving

whether it is indeed effective for a number of indications related to soft tissue injuries.

Proving statistical significance for broad patient populations can also be a problem, although the clinical researcher has reportedly observed positive effects in certain types of patients. Furthermore, there is the requirement of tedious and meticulous record keeping since all raw clinical data rather than detailed summaries must be submitted to the FDA. FDA is also highly concerned about the effects of drugs on long term use.

In general, drug sponsors and clinical researchers think the later stages of clinical research are too long. FDA cannot hope to establish whether the drug causes a low incidence of safety problems (e.g. less than 1 in 1000) when hundreds or a few thousand patients are in Phase III studies. Using more patients is not practical. Low incidence safety problems are better established through post-marketing surveillance. Better post-marketing surveillance is also regarded as an important step by consumer activist groups. In fact there appears to be little opposition to post-marketing surveillance as long as it does not become a highly tedious all inclusive process.

(*d*) *FDA guidelines for NDA's are not precise and are therefore subject to various interpretations*

FDA guidelines are vague regarding the documentation to be submitted with an NDA. This may cause some reviewers to use personal preferences and standards which differ from reviewer to reviewer. Reflective of this problem may be the GAO finding that 76 percent of the NDA's submitted in 1975 were returned to the sponsor one or more times for additional data.

Confusion has occurred in regard to the use of data from foreign clinical studies in the approval of a new drug and the requirement for domestic verification. FDA officials have vacillated on the requirement for domestic verification but now seem to require that some U.S. studies be conducted. Sodium valproate represented a vivid example of the confusion within the agency on this topic. Some industry officials say that FDA reviewers require more detail today on chemistry and manufacturing controls than they did previously, although the guidelines for the submission of such information have not changed since 1971.

Industry does not think the FDA's animal testing guidelines are consistent with the state-of-the-art.

FDA regulations require that studies demonstrate whether or not a drug is effective for its intended use. They do not require that the drug be as good as or better than other available drugs. This is an important point because some think that FDA staff sometimes appear to be using the latter as a requirement.

The subcommittee concludes that more specific guidance on the preparation and submission of NDA's would be helpful to sponsors and would tend to speed up the drug approval process.

(*e*) *Domestic verification of foreign clinical studies*

In 1975 the FDA published regulations relating to the acceptability of international clinical research in support of a new drug application. These regulations state that adequate and well-controlled trials supported by case reports will be accepted on the same basis as such

trials conducted in the United States. 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.

In practice, this results in the requirement that drugs be approved on the basis of clinical trials (two or more) conducted in the United States. Although FDA states that many drugs are approved primarily on the basis of foreign data, the subcommittee finds that foreign data is regarded as meaningless until some U.S. studies are also conducted. FDA's failure to approve any NDA's on the basis of foreign data alone, regardless of its quality, has led to the delay in the introduction of new drugs in the United States. If a country accepts adequate and well-controlled studies from another country without domestic verification, it can result in earlier introduction of a drug in that country. Another compelling reason for acceptance of data from foreign clinical trials is that current information on, and up-to-date practice of, the science and the art of the conduct of clinical trials is becoming universal.

Sodium valproate is a case in point. There were over 200 favorable reports in the medical literature on the effectiveness of sodium valproate in the treatment of epilepsy. Thirty of these were clinical scientific studies involving a total of more than 1,300 patients. It is extremely unusual for even a U.S. drug to have undergone such widespread investigation before marketing. FDA's Neurological Drug Advisory Committee reviewed these studies, and the committee's chairman reviewed them. Both reviews found that at least two studies were adequate and well controlled and clearly demonstrated valproic acid's effectiveness and safety in controlling absence seizures in epilepsy and unanimously recommended that the FDA immediately approve the drug.

FDA staff questioned aspects of the studies and required that at least one U.S. study be conducted. When completed this study showed nothing significantly different from the foreign well controlled studies. The result was several more months delay in the approval of the drug in the United States. Sodium valporate is one of a few, if not the only drug which the FDA has approved on the basis of just one U.S. study accompanied by foreign studies.

FDA and some clinical researchers have been concerned about differences in the quality of U.S. trials compared to foreign clinical trials. But GAO finds that drug sponsors today design clinical trials to meet the most stringent requirements. Further regulations in technically advanced countries are moving closer to those in the United States. FDA Commissioner Kennedy said the U.K. adopted in 1977 an efficacy requirement similar to our own. Sweden, Australia and Canada now have requirements for animal and clinical studies for safety and effectiveness that are very similar to our own. Japan is currently considering comprehensive amendments to its legislation. Germany strengthened its drug law in 1976 and has adopted the equivalent of investigational new drug (IND) provisions.

GAO found that European countries have a greater tendency to accept foreign clinical data without domestic verification. However, the acceptance of foreign data, and the extent of domestic verification of this data, varies from country to country. Some countries—Norway,

Netherlands, Switzerland—may accept foreign test data without domestic verification, depending on its source. The United Kingdom, and Sweden will usually request domestic verification. The subcommittee finds that the FDA always requires domestic verification.

One of FDA's prime reasons for requiring U.S. clinical trials is because of what it regards as differences in the U.S. medical care system. "Because the purpose of clinical trials of a drug is to evaluate safety and effectiveness under conditions of use that resemble those in our own health care system, we normally require that one of the critical studies on a new drug have been done here," Commissioner Kennedy testified.

No doubt differences in the total system exist but in regard to the safety and efficacy of drugs medical experts disagreed with FDA thinking. They could not subscribe to former Commissioner Kennedy's assertion that differences in medical practices in the United States and Western European countries require the conduct of at least a few studies in this country. The populations do not differ sufficiently to warrant a general assumption that the reaction of foreign nationals to a drug will invariably be somewhat different than the reaction of U.S. nationals.

The subcommittee concludes that a mechanism needs to be established within FDA to evaluate foreign clinical data collected by sponsors in order to determine on drug-by-drug basis whether it meets the intent of U.S. criteria and can be used in lieu of domestic data.

(*f*) *Compassionate IND*

If a drug is under clinical investigation, FDA has a procedure called a "compassionate IND" which can be utilized to make unapproved drugs available to physicians whose patients have no other alternative therapy available. However, the process for obtaining a "compassionate IND" is so cumbersome that most physicians give up rather than going through the extensive paper work required by FDA. The process is also generally slow and not useful for emergency situations.

For example, Dr. Connolly sites the case of the diuretic Minoxidil:

> Minoxidil has, in theory been available on a clinical trial basis for seriously ill patients for some time in this country, but . . . the burden of documentation and other paperwork which the FDA demands (for a compassionate IND) was such that busy clinicians just could not cope and consequently in practice were unable to use the drug. Necessarily patients suffer as a result of this. Considering how serious the plight of many patients is, in whom one would consider the use of such a drug, it is a pity that the regulatory authorities could not take a more realistic view of risk and benefit and relax their stringent requirements.

It is important, therefore, for FDA to reduce the paperwork and other burdens associated with "compassionate INDs" in order that drugs, currently only available on a restricted basis, can be made available to those relatively few individuals with certain life-threatening illnesses ("orphan diseases") for which the industrial cost threshold is sufficiently high to preclude marketing. In these instances, benefits vs. risks assessment has to be more aggressively applied for the se-

lective approval of "compassionate INDs." In this and in similar situations, the subcommittee believes hat a tiering of the drug regulatory requirement for approval should be made in terms of the size of the population critically ill, of benefits vs. risks, of the scale of the distribution for the drug, and alternatives available to the affected population. Mechanisms for expeditious regulatory agency actions on "compassionate IND" drug requests are essential if the wellness of affected U.S. citizens is to be improved. Proposed drug regulatory reform legislation suggested "breakthrough provision" may be one approach.

C. International Differences

1. USE OF EXPERT OR ADVISORY COMMITTEES

FDA routinely uses expert committees to advise them on the merits of drugs. In the United Kingdom primary reliance is placed on the advisory panel, and people working for them are functioning as staff people who prepare the material to be reviewed by the experts. Often FDA does not follow the advice of its advisory committees. This is in great contrast to European countries which place considerable reliance on the use of expert panels and expert opinions and rarely override their decisions. In this country, advisory committees, for the most part, are only given lip service, and the FDA makes the final decision itself. In the United States, an increasing trend is that conflict of interest requirements are disqualifying many experts from serving on review committees and from participating in the drug approval process.

With FDA's move to greater public involvement, patients' views and needs have not been adequately represented on review committees.

More effective use of expert committees focusing on patients' needs could help speed up the drug approval process. In addition to facilitating the FDA drug review and approval process, Gregory Ahart of the GAO noted:

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

2. PUBLIC DEMAND FOR OPENNESS IN DECISION MAKING AND DUE PROCESS REQUIREMENTS

Another factor contributing to the slower drug approval process in this country is the increasing insistence on openness and due process. The emphasis on openness in drug decisions is probably as great as in any other area of public concern. The most obvious manifestations of public demands for openness and due process include: open meetings of FDA drug advisory committees; substantial increases in FDA freedom-of-information request; mounting numbers of consumer and industry petitions; requests for hearings; law suits demanding action or challenging Agency decisions on drugs; and agressive oversight hearings by the Congress. Although these factors unquestionably mitigate against speedy drug approvals, FDA generally re-

gards them as healthy trends that produce valuable intangible benefits such as greater public participation and understanding of drug benefits and risks.

Foreign drug approval processes are closed to public participation which undoubtedly allows them to proceed more expeditiously.

The subcommittee believes openness is important but it should not become a vehicle by which extreme points of view of the healthy can delay the availability of a useful drug to the sick and dying people in our country.

3. USE OF APPROVED DRUGS

There are several differences in the U.S. health care system and the way technically advanced European countries can follow and regulate the use of approved drugs. FDA claims that the lack of commonness in regulatory and approval processes causes them to be more careful and thus slower in approving drugs in the United States. The greatest differences in this respect appear to exist between the United States and the United Kingdom. Although these are formally recognized differences, the differences can be accommodated within FDA's existing mechanisms of operation without compromising FDA's mandate.

(a) Some European countries have better postmarketing surveillance programs

The objective of a post-marketing surveillance is to monitor the use of a marketed drug to identify uncommon adverse reactions and to obtain more information on incidence of reactions already identified in clinical trials. In most countries GAO, visited and in the United States, post-marketing surveillance consists of spontaneous reporting from physicians, hospitals, or manufacturers; and selected hospital monitoring. U.S. law forbids the FDA from requiring physicians to report on adverse reactions but FDA does require drug sponsors to report. In recent years more complex post-marketing surveillance on the part of the sponsor have been a condition for approval to market a drug or medical device.

GAO testified that the United Kingdom, unlike most of the other countries, has a formal followup procedure for adverse drug reaction reports and is able to protect the confidentiality of the reporting source. Because of this, according to a United Kingdom drug regulatory official, participation by physicians is greater in the United Kingdom than in other countries. The post-marketing surveillance reporting system has a positive effect on the drug approval process because it gives the regulatory agency more confidence in being able to accept a lower number of clinical trials in the testing stages of new drug development.

The United Kingdom "yellow card" post-marketing surveillance system is, however, limited. Its greatest asset is to obtain more information on the incidence of reactions already identified. A major requirement for post-marketing surveillance should be data analysis to identify other, perhaps uncommon, adverse reactions as well.

The subcommittee strongly supports the need for better post-marketing surveillance. It must be conducted in a practical way, however, which does not become highly tedious and costly as would post-marketing surveillance for every patient on every drug.

(*b*) *European countries have more flexibility to limit use of a drug*

In the United Kingdom, the drug approval agency can restrict or limit a drug's use in a variety of ways. It may, for instance, limit the use of a drug to a hospital setting or restrict prescribing authority to certain types of medical specialists.

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

However, U.S. law does not permit restricted distribution. Therefore, FDA believes it is important that adequate evidence be available at the time of marketing approval. Accordingly, this allows FDA to have a significant level of confidence that a drug is safe and effective for the large patient population which will receive it.

(*c*) *Review of marketed drugs*

The United Kingdom periodically reviews marketed drugs to determine if continued use is appropriate. A panel of experts appointed by the Committee on the Safety of Medicine, the British drug approval agency, reviews the country's experience with the drug and with any adverse side effects resulting from the use of that drug.

Thus, a drug, once licensed, does not necessarily remain on the market indefinitely without followup reviews. The United States does not follow a similar procedure. But the U.S. law does provide FDA with mechanisms to remove hazardous drugs from the market.

4. SPONSOR-AGENCY RELATIONS

Government and industry officials in the countries the GAO visited characterized their relationship as cooperative. They could not visualize a smooth working drug approval process under an adversary relationship. While unable to say how much this contributes, GAO believes it is a factor in producing a speedier approval process. As indicated earlier, impact of consumer involvement in other countries on the drug approval process is minimal.

In the United States the FDA projects a strong attitude of distrust toward sponsors (industry) and clinical researchers. Dr. Connolly stated:

> Clinical medicine is conducted in a far freer atmosphere in England than here. While I believe it is true that once a drug is approved here the FDA cannot by law restrict the way it is used, the FDA admits this grudgingly. Physicians are often reluctant to use agents other than as approved by the FDA for fear of malpractice suits. Several members of the American legislative bodies have in the recent past expressed a desire to limit by law the ways in which a physician may use a drug. The implication seems to be that doctors are not to be trusted, and that the politicians must put chains on the charlatans to keep them from doing malicious harm. I believe this to be wholly inappropriate. While there are bad members in any community the vast majority of American physicians are high minded people intent on doing their best for their patients. Attempts to frame laws to cope with each bizarre aberration at best, produce a paralyzing milieu.

The old adage that "hard cases make bad laws" is relevant here. In England there is much greater sense of trust between the legislature and the physician. Once a drug has gone through a reasonable screen for toxicity and efficacy the attitude seems to be "You're the doctor. You are trained to deploy drugs for your patients' benefit. Here is a new drug which we consider safe. Get on and use it as you see fit." This leaves hope for the inventive and creative use of drugs as well as providing opportunity for following up the fruits of serendipity. If Congress feels that American physicians are not worthy of such trust (I cannot believe that this is so) the answer would be better training of physicians, not more FDA rules.

5. NEED FOR INTERNATIONAL COOPERATION

(*a*) *Exchange of safety and efficacy data between drug approval agencies*

Donald Kennedy noted:

> Science is international, and high quality scientific data on drugs should properly be acceptable in any nation in the world. The country from which such data originate is irrevelant to its quality and its usefulness to mankind.

Commenting on the current state of FDA William Wardell also indicated:

> Regulatory requirements for the repetition of experiments where the outcome is already known (either from foreign or domestic studies) are ethically unsound for the patient and the investigator, and may even put the regulatory agency at legal risk."

Earlier in this report (see IV, B, e), the potential for redundancy in the domestic verification of foreign clinical studies and trials was discussed. In addition to the scientific and ethical concerns raised above in having a regulatory agency which fosters a level of scientific and clinical testing and replication that exceeds reasonable requirements, the existing situation raises a number of economic factors related directly to industry drug investment decision making that may ultimately have a profound influence on the availability of drugs for "orphan diseases", and on development of innovative new drugs. Proposed drug regulatory reform legislation may offer some promise in the exchange and acceptance of drug data from foreign sources.

(*b*) *International approval of drugs*

More fundamental to the issues raised previously is the need to develop the necessary links between the FDA and responsible international organizations, such as drug regulatory authorities of the European Economic Community (EEC) and other countries, the World Health Organization, (WHO), and the Pan American Health Organization (PAHO), to resolve differences in or distinctions between drug review and approval approaches and procedures, and to

implement a system for international aproval of drugs. Initially this means that FDA must, with the cooperation of international organizations and industry, clarify and simplify its procedures for acceptance of data from foreign studies. Further along it is hoped that an international consortium of drug regulatory authorities will develop criteria within a regulatory framework for guiding international acceptance of drug data from safety and efficacy studies irrespective of participating country of origin.

V. EFFECT OF THE DRUG LAG ON INNOVATION AND PRODUCTIVITY IN THE PHARMACEUTICAL INDUSTRY

The drug lag reflects fundamental problems in the U.S. process of pharmaceutical innovation. It appears that the United States is losing its leadership role in drug discovery. Even when drugs are discovered in the United States, nearly half of the clinical studies for these drugs are carried out first abroad. Furthermore, the slow, complex and expensive drug development and approval process has driven most small companies out of the field of innovative discovery research. The number of research intensive pharmaceutical companies has now decreased to about 25–30. Productivity of all companies is limited to some extent by inflexible U.S. export policies. The more pressing problems that the subcommittee found are discussed below.

A. More Resources Are Being Devoted to Regulatory Matters

A company can allocate only a limited portion of its finite revenues to research and development. Research intensive pharmaceutical companies, commonly allocate about 10 percent of their pharmaceutical sales toward research and development. This is much more than most industries. In the past two decades, increasing regulatory requirements and increased data requested by the FDA to establish safety and efficacy mean that the percentage of the annual pharmaceutical R. & D. budget devoted to innovative research has decreased and the percentage to handle regulatory matters has increased. In essence this requires more scientists to become involved with supportive rather than innovative discovery research in the pharmaceutical industry.

Again the subcommittee finds safety and efficacy are important requirements not to be minimized. However, FDA should carefully assess its requirements to eliminate the need for non-productive or redundant research that wastes valuable scientific resources. Industry maintains that many of the increased regulatory requirements have not improved FDA's ability to make judgments about safety and efficacy. GAO and other witnesses in essence support this.

Once an investment of $30–50 million has been made and the NDA is filed with the FDA, it is a further drain on financial resources to wait an excessive amount of time, as is often the case, for FDA approval. In this respect the slow FDA approval process can discourage innovation because it usurps industry's much needed technical and financial resources to promote future discoveries.

Some consumer groups charge that FDA's slower process may in fact have a positive effect by helping industry's credibility and saving it from lawsuits. However the GAO found:

> In our opinion, most unsafe drugs are culled out by industry rather than being submitted to FDA. For example, we expect drug manufacturers to discontinue clinical testing

where serious questions of safety are identified. In addition, other drugs are likely to be eliminated by FDA's requests for additional information on safety questions.

In the end most of NDAs that sponsors continue to pursue are approved by FDA. It is just that FDA takes a much longer time to do this than its foreign counterparts.

B. The Number of NCE-INDs Filed By U.S. Firms Is Declining

One of the most useful measurements of pharmaceutical innovation, at an earlier stage than drug approval or marketing, is the flow of new chemical entities (NCEs) into human investigation. This is determined by considering the number of NCE-IND's filed with the FDA by U.S. firms.

1. NEW CHEMICAL ENTITIES (NCES) DISCOVERED BY U.S. FIRMS IS DECREASING

Wardell's studies show that:

> The annual rate of IND filings for U.S.-owned NCEs generally declined from 1965 to 1972, whereas the rate was fairly constant for foreign-owned NCEs over the entire period from 1965 to mid-1975.

Since 1972, the average number of NCEs taken into human investigation by U.S. firms declined sharply (by 40–45%) during 1975–1976.

(*a*) *Increased regulatory requirements divert innovative research*

Increased regulatory requirements which divert drug industry innovative research resources, a major reason for this decline, was discussed above.

(*b*) *The number of research intensive pharmaceutical companies is decreasing*

The number of pharmaceutical companies able to afford to maintain full-scale research operations aimed at the discovery of pioneer new drugs or NCEs has been decreasing. Today only about 30 such firms are found in the United States. Of these, the portion of the U.S. industry responsible for the NCEs taken into human testing is relatively concentrated; 7 of 36 companies account for about half of the NCEs and 4 account for about one-third.

On a possible positive note, industry concentration has been growing. These larger companies may be able to carry out more efficient research programs than small companies. How this can be extrapolated to the number of NCEs is uncertain. One cautionary note about increasing industry R&D concentration is that several studies have shown the increased innovative capabilities of technology-intensive small companies. The necessity to make significant commitments for increasingly higher R&D costs for a decade or more appears to be a major facor causing a decline in the number of small companies able to maintain research programs aimed at pioneer new drugs. This may, in turn, be a contributing factor to the decrease in the number of NCEs and reflect a decline in the innovation potential and capabilities of the industry as a whole.

(c) *U.S. firms rely on foreign sources for some NCEs*

Wardell's studies also show a disturbing trend that U.S. firms are getting an increasing number of NCEs from foreign firms.

> Considering all NCE–IND filings by U.S.-owned firms, the proportion that were self-originated (as opposed to those obtained from other sources, e.g., by licensing from foreign firms) fell sharply, from about 80 percent or more in the previous nine years to 63 percent for those filed in 1976.

(d) *Knowledge depletion hypothesis*

FDA claims a major reason for the decline in the number of NCEs is that new scientific knowledge regarding disease and drug development has been depleted. Medical researchers and industry uniformly deny this. With the general explosion of scientific publication over the past two decades, the advances in molecular biology and sophisticated instrumentation techniques, the subcommittee can not accept the knowledge depletion hypothesis as a cause for the decrease in the number of NCEs.

2. IND FILING IS DECREASING

Wardell's studies show that the general decline in the average number of IND filings by U.S. firms from 1962 to 1972 continued and in 1975 and 1976 decreased below the previous low observed in 1972.

The major factors for the decline in the number of IND's are the decrease in the number of NCE's coupled with the fact that an increasing number of United States discovered NCE's are being researched abroad.

(a) *U.S. firms are conducting an increasing number of clinical studies abroad*

In the 1960s and 1970 Wardell's studies show that the percentage of NCEs first studied in man abroad by U.S. firms continued to rise reaching 44 percent in 1976. Since nearly 90 percent of the NCEs studied in man are dropped prior to NDA submission, most of the U.S. NCE's for which clinical research is started abroad will never return to have an IND filed in the United States. This raises a more serious problem about future U.S. based role in innovative drug and clinical research. In addition, employment of U.S. professionals in this area is not as large as it could be.

There are a number of reasons why American companies do scientific investigations overseas. They relate either directly or indirectly to FDA regulations. First, there is a greater ease in commencing and carrying out Phase I and II studies in other countries. This does not appear to be because of lower ethical standards but simpler procedures to achieve them. This is important because it allows an earlier determination of a drug's effectiveness or ineffectiveness. Whether a new agent is effective in humans is the most critical question to answer in the pharmaceutical innovative process. The reason these early studies can be initiated sooner abroad is that no regulatory approval is required, for example in the United Kingdom. In these countries, the investigator, study institution, and sponsor accept total responsibility for the studies. The drug approval agencies in the U.K. have minimal involvement in the early stages of clinical research.

Second, studies abroad are more economical. Cost of wages, equipment, supplies and paperwork are much less lower. Third, it is easier to conduct clinical studies overseas. Less extensive regulations mean informed consent is less formalized. The fact that GLP or GCPs regulations do not need to be addressed allow the clinical research process to move more quickly. Finally when the time comes to seek approval of a drug, the European agencies are less formalized in their review of case records and more willing to accept summaries of data prepared by experts. GAO found that these agencies usually respond more quickly to approving a submission.

An example of the movement of clinical research abroad and the reasons were cited by Mr. Hoff:

> About 22 percent of Upjohn pharmaceutical research manpower is located abroad. In 1975, approximately 14 percent was located abroad. This figure is expected to rise to something beyond 25 percent in the early 1980's. Clinical research efforts can be considered to be proportional to research manpower. Since 1962, exactly half of the new chemical entities developed by Upjohn were marketed abroad first. An increasing number of Upjohn new drugs will be introduced initially in overseas markets. The reasons for this include: (1) our rapid growth of overseas markets, and (2) the greater speed of drug approvals in some foreign countries.

C. Other Drug Industry Innovation Disincentives

1. EFFECTIVE PATENT LIFE FOR DRUGS IS DECREASING

In a study of new chemical entities that received NDA approval from 1966 through 1977 Wardell found that the average effective patent life decreased from 13.8 years in 1966 to 8.9 years in 1977. By law the duration of a U.S. patent is 17 years. Since patents often issue 2–4 years after the discovery of a drug and since it takes 7–12 years from discovery to obtain marketing approval, the patent holder will only have 7–13 years of patent protection remaining after the drug has been approved by the FDA. Decreasing patent life has been due largely to increased drug approval time and the time required to initiate and complete clinical testing. Drug research disincentives increase as drug approval time similarly increase. This is particularly true in areas where clinical testing and FDA approval are likely to take longer than normal.

2. FDA RELUCTANCE TO APPROVE DRUGS OF GIVEN TYPES OR FOR CERTAIN DISEASE AREAS

If FDA develops a record for not approving drugs in a given disease area, this can serve as an industry-wide disincentive to do research in that area. A research organization simply will not conduct research in areas where a product will not be approved. The area of antihypertensive drugs is a case in point. When FDA did not approve any new pioneer antihypertensive drugs for a decade, beginning in the early 1960's to the early 1970's, firms began to question whether they should continue research in this area. Even companies which spent years of

R&D prior to filing for FDA approval in these areas have had to seriously consider abandoning investments in these areas because of the lack of prospects to recoup R&D and other investments made due to further delays anticipated in FDA's approval process and to further reduction in the useful life of patents. The agency attitudes repressed and delays encountered will hopefully not be repeated in the future.

3. DRUG EXPORT LAWS INHIBIT U.S. PRODUCTIVITY

Present drug laws do not permit U.S. firms to export drugs unless these drugs are first approved by the FDA. There are a few exceptions, such as antibiotics. The concern for the welfare of people in other countries is necessary and humane but the lack of flexibility in the drug laws causes problems in the development of drugs for many parts of the world, dampens productivity in the U.S., reduces U.S. international trade competitiveness in technology-intensive fields, impacts negatively our already troublesome balance of payments deficits, and may, in fact, be counterproductive to our national economic and social goals.

(a) U.S. manufacturers build production facilities overseas.

Worthwhile drugs are not limited by geographic boundaries. If there is a need in another country and that country has approved a U.S. discovered drug, it will generally become available whether or not the U.S. has approved it. If not approved in the United States, this can occur by a U.S. firm either building manufacturing facilities abroad or licensing the drug to a foreign manufacturer.

The "Drug Lag" occurs because foreign agencies generally approve drugs sooner than the FDA. After an investment of $30–50 million and approval of a drug by a foreign agency a U.S. firm can hardly be expected to wait months to years longer in order to first market the drug and begin to recoup its investment. Since U.S. laws forbid the export of the drug, the U.S. manufacturer will generally build foreign facilities to market the drug. This is unfortunate because when the drug is later approved in the United States these facilities remain in operation abroad. The result is that the United States has lost another exportable product which could provide more U.S. jobs and contribute to a more favorable U.S. balance of payments. Alternatively, if the U.S. firm does not have the resources to market the product abroad it will most likely license it to another U.S. or foreign firm that does have the resources.

(b) U.S. companies are limited in their ability to develop drugs for diseases not common to the United States

The export law coupled with FDA's policy not to approve drugs unless domestic clinical trials have been conducted means that a U.S. firm without foreign facilities will not be able to export a drug for diseases not endemic or common to the United States. For example, there is no opportunity to conduct clinical trials in the United States for most tropical diseases. Therefore, drugs for these diseases will not have FDA approval and will not be exportable. This is unreasonable in light of the U.S.'s increasing interest in international health and in providing access to increased health care technologies to less developed countries. The subcommittee believes that FDA could develop mech-

anisms similar to those suggested for "compassionate INDs," including reduced testing requirements and criteria for restricted distribution, in order to make certain drugs available to the sick and infirm of foreign countries, for which no or inadequate therapy currently exists.

The subcommittee believes that the drug lag does limit innovation and productivity in the pharmaceutical industry. Further hearings into the details and magnitude of this effect are recommended.

CONCLUSIONS

In its review of the drug approval process of the FDA the Subcommittee has limited its investigation to the Bureau of Drugs only and notes that the Bureau zealously carries out its mandate to protect the public from unsafe or ineffective drugs. In carrying out this charge, however, speed with which the FDA reviews and approves drugs has been a continuing target of criticism not only by drug manufacturers seeking to market these drugs but also by physicians wanting to use new therapeutic advances and consumers, either patients wanting the benefits of new therapeutics or others, concerned about protection from unforeseen side effects.

A recent GAO assessment of the FDA drug review and approval process provided in hearing testimony represents the first major independent evaluation of the decade-long controversy often referred to as the U.S. "drug lag." Data for this assessment by the GAO was obtained by extensive review of FDA records, discussions with FDA personnel, visits to drug agency authorities in nine foreign countries, visits to several pharmaceutical firms, and visits to numerous medical professionals.

GAO and other testimony provided at these hearings substantiated earlier impressions that introduction of some important drugs into the mainstream of health care is being delayed and a U.S. "drug lag" does exist.

Several factors and decision points within FDA's drug approval process have contributed significantly to this delay. The IND represents a major portion of this time. Even FDA's proposed objectives to speed up the drug approval process will neither meet the six month period which Congress intended nor make it faster than processes in other technically advanced countries.

The delays resulting from FDA testing and other requirements have not consistently reduced the risk associated with market release of a new drug when compared with other technically advanced countries or increased the benefits contributing to wellness in the U.S. population. As a result of the delays, U.S. patients have suffered a number of significant therapeutic losses for periods of months to years and sometimes even a decade. Hearings' testimony identified more than 30 significant drugs for cardiovascular diseases and a dozen drugs for neurological diseases which had been delayed over the past two decades.

FDA has a number of management deficiencies (for example, poor communication, uneven workload, inadequate guidelines, adversarial relationship with industry, ineffective use of computer information systems, and poor coordination of segments of the drug review and approval process) that have exacerbated delays in drug approval.

FDA should draw from processes and mechanisms used by foreign approval agencies in expediting the drug approval process, such as use of committees of experts (such as physicians, academicians, paraprofessionals and consumer representatives) in the drug approval

process, acceptance of some foreign data without requiring domestic verification, more cooperative relationships between approval agencies and drug sponsors, and various mechanisms for post-marketing surveillance.

Delays in the FDA drug approval process and subsequent reduction in the patent life of drugs may discourage pharmaceutical industry innovation and reduce U.S. world technological leadership in this area not only by increasing the time required to bring a pioneer new drug to market but also substantially increasing the investment risk and costs for new drug research and development phases.

Further congressional oversight is needed to see that deficiencies resulting in the "drug lag" are corrected and that FDA policies reflect a reasonable approach to bringing new drugs expeditiously to the market.

RECOMMENDATIONS

1. *Promote better post-marketing surveillance programs.*—The Administration bill (S. 1045 and H.R. 4258) and the Kennedy bill (S. 1075) authorize the Secretary to establish such programs but do not spell out any specifics. Attention needs to be given to freedom of information laws. A change to protect physicians from prosecution if they supply information to FDA may be needed.

2. *Give FDA a lesser role in the early aspects of clinical research and testing.*—The safety record in early clinical testing is very good. Therefore it is logical to give more authority to institutional review committees to approve proper protocols. This could shorten the longest stage of the drug development process, the clinical research and testing stage, which now takes four to six years. S. 1075 appears to be moving in this direction.

3. *Give expert panels a stronger role on decisionmaking on the approval of new drugs.*—The Administration bill (S. 1045 and H.R. 4258) and the Kennedy bill (S. 1075) simply recognize advisory committees as they are used today. However, these committees have no power. Conflict of interest requirements might be modified somewhat to permit the most knowledgeable experts to serve on these committees provided the Commissioner determines that the position of the committee member is not compromised.

4. *Give more weight to data from well controlled foreign clinical studies.*—Although the FDA states it has been its policy since 1975 to accept data from foreign clinical studies, no drug has been approved in the United States on the basis of foreign studies alone. In fact, few drugs have even been approved on the basis of one U.S. study plus foreign studies. For many drugs this appears to be a needless duplication of efforts and a waste of scientific resources.

5. *Establish a procedure whereby drugs for crisis ills (life threatening diseases) are expedited.*—Present FDA regulations provide for a "Compassionate IND" but it is cumbersome for physicians to obtain. S. 1075 contains a "breakthrough provision" which is a step toward making drugs of this type available sooner.

6. *Establish a simple procedure whereby small numbers of patients and physicians can obtain drugs not yet approved by the FDA—Drugs for "Orphan Diseases".*—Insufficient market potential compared to high development costs dictate that such drugs may not even be under an IND for testing in this country. Where there is reasonable scientific evidence of safety and efficacy through studies elsewhere in the world, small numbers of U.S. patients should be able to get these drugs legally. A "Compassionate NDA" is suggested. S. 1075 requires that the Secretary promulgate regulations exempting the administration of drugs to small numbers of patients with serious health problems. Hopefully these regulations and the three year limit will not be so tedious as to prevent effective use of this procedure.

7. *Encourage flexibility in the U.S. pharmaceutical industry by allowing export permits for drugs approved in other countries.*—Present law requires a drug to be approved by the FDA before it can be exported. Section 134 of the Kennedy bill (S. 1075) appropriately addresses this issue.

8. *Encourage better management practices at FDA.*—FDA has a personnel and attitudinal problem as much as an organizational or legislative problem. Improvements in this area include a need for an evaluation of the quality and performance of reviewers; retention of the same reviewers throughout the review; possible use of the NSF rotator concept as a mechanism to bring new ideas into the agency; clearer guidelines for approving new drugs; better use of automatic data processing systems; and better communications with industry.

9. *Establish or strengthen an "ombudsman" capability within FDA.* A high level office should have the purpose of promoting and tracking the progress of all aspects of the drug approval process and of maintaining good communications with industry, consumer protection, and health groups. The office should also keep abreast of significant drug advances in other technologically advanced countries and act as an advocate within FDA to encourage early testing and introduction of significant new therapeutic advances in this country. This may require a broader definition of the FDA's purpose as a consumer protection agency. Such a definition should focus more on protection of the consumer from the consequences of disease.

10. *Establish a simple and expeditious appeal system for resolving scientific disputes.*—The purpose of this system would be to provide a quick mechanism to resolve scientific disputes inside and/or outside of the FDA. Senator Kennedy's bill (S. 1075) presently calls for "the Secretary to promulgate regulations establishing informal and expeditious procedures for the impartial review and resolution of scientific disputes during the course of a drug investigation".

11. *Promote international cooperation and exchange.*—Exchange of animal safety and human safety and efficacy data between international drug approval agencies would eliminate needless duplication of efforts and waste of scientific resources while moving toward an "International Stamp of Approval" for drugs.

12. *Lower innovation disincentives through patent reform.*—The extension of effective patent life to counter significant FDA delays in decision making would increase potential investment return and thereby encourage pharmaceutical industry innovation in the United States.

APPENDIX A

COMMITTEE ON SCIENCE AND TECHNOLOGY,
U.S. HOUSE OF REPRESENTATIVES,
Washington, D.C., May 9, 1977.

Hon. ELMER B. STAATS,
Comptroller General of the United States, General Accounting Office,
Washington, D.C.

DEAR MR. STAATS: On April 6, 1977, I and my Subcommittee Staff Director, William G. Wells, Jr., met with several General Accounting Office individuals to discuss serious operational problems at the Food and Drug Administration. They were Messrs. McGough, Jojokian, Morris, and Ingram.

I realize, as the enclosed article points out, that there have been some one hundred Congressional investigations and fifty highly critical reports by the General Accounting Office concerning the Food and Drug Administration. Clearly, the situation described in the enclosed article cannot be permitted to continue. Dr. Kennedy may well have a new strategy for dealing with the problems of the Food and Drug Administration, but I believe also that the competence of the General Accounting Office might well be applied to helping improve what is currently an intolerable situation from the point of view of the public and the Congress.

I would, therefore, like the General Accounting Office to undertake a review to determine what problems exist and what improvements can be effected in the area of drug approval. This review should be directed at, but not limited to such questions as:

1. Is there an inordinate delay in the processing and approval of new drugs for marketing in the United States? Consideration should be given to the need to improve management and administrative processes, and to apply innovative computer technology to redress existing inordinate delays, and rationalize the decision-making process.

2. Has the delay of new drug approvals adversely impacted on the introduction into the United States of therapeutically important drugs that are available in other countries? What are the risk-benefit factors here?

3. What improvements can be made in the Food and Drug Administration's risk-benefit analysis involving new drug approvals? How does the agency's risk-benefit analysis compare with similar analyses performed in other technologically developed countries?

I believe that the situation described in the enclosed article impacts on the quality of program performance and that structural improvements in the administration of new drug approvals—including the decisionmaking process itself—could contribute to improving the existing situation at the Food and Drug Administration.

Sincerely yours,

JAMES H. SCHEUER,
Chairman, Subcommittee on Domestic and International
Scientific Planning, Analysis, and Cooperation.

APPENDIX B

The Drug Regulation Reform Act of 1979

Summary of S. 1075*

As approved by the Committee on Labor and Human Resources, United States Senate, S. 1075 would—

(1) Extend the scope of the Federal Food, Drug, and Cosmetic Act (hereinafter referred to as the Act) to drugs that are processed, manufactured, distributed, held for sale, and dispensed entirely within a single State, if these activities also affect interstate commerce. The Act would not apply, however, where such processing, manufacture, distribution, holding for sale or dispensing are authorized by State law;

(2) Prohibit a generic prescription drug in solid form (tablet or capsule) that is identical in color, size, and shape to an originally marketed drug from being marketed unless the generic drug clearly bears on the drug itself the name or trademark of its manufacturer or distributor;

(3) Eliminate the concept of "new drug" and, together with other provisions, establish a single regulatory system for all drugs marketed in the United States. The effect of this provision, together with amendments to the drug approval process, is to make all drugs, with certain narrowly defined exceptions, subject to the approval process and the concomitant regulatory controls;

(4) Prohibit the submission to FDA, or to another person knowing that it may be submitted to FDA, of any application, report, or other document that contains a false or misleading statement of a material fact;

(5) Authorize FDA to embargo for a period not to exceed 30 days a drug believed to be adulterated, misbranded, or otherwise subject to seizure;

(6) Amend the criminal provisions of the Act to establish a negligence standard in lieu of the existing standard of absolute liability. Also, the amount of fines that could be levied for criminal violations of the Act would be increased to $50,000 for individuals and $100,000 for businesses;

(7) Expand the adulteration provisions of the Act to include a drug that fails to meet a compendial standard relating to identity or stability or a standard established by FDA relating to bioavailability;

(8) Require that the label for prescription drugs include the name and place of business of the manufacturer and distributor;

(9) Eliminate from the current misbranding provisions of the Act certain exemptions for drugs dispensed by prescription;

---

*Report (No. 96–321) of the Committee on Labor and Human Resources, United States Senate on The Drug Regulation Reform Act of 1979 (S. 1075), September 18, 1979.

(10) Require the manufacturer or distributor of a drug to prepare information labeling for patients;

(11) Require persons selling drugs at retail to post the prices of the 50 most frequently sold prescription drugs;

(12) Require the manufacturer or distributor of a prescription drug to prepare information labeling for distribution to practitioners and to distribute this information to practitioners when promoting a drug during personal visits to practitioners;

(13) Provide for the development and distribution to practitioners and others of a Federal prescription drug index;

(14) Authorize FDA in special circumstances to require a manufacturer to notify patients and practitioners regarding a risk posed by a drug;

(15) Authorize FDA to establish educational programs regarding the safety, effectiveness, and proper use of drugs;

(16) Establish requirements for prescription drug advertising and authorize FDA to review such advertising during the 90-day period in which a drug is first promoted;

(17) Authorize FDA to require correction of prescription drug advertising that is false, misleading or incomplete;

(18) Impose limits on drug promotion by: prohibiting drug manufacturers or distributors from giving gifts valued at more than $10 to practitioners, students of the allied medical professions and sciences, or members of their immediate families; limiting the distribution of free drugs; and requiring disclosure of sponsorship of drug educational activities;

(19) Restrict access to, and disclosure of, information contained in prescriptions that are on file with a pharmacy. The Bill would permit use of such information, upon deletion of individually identifiiable personal data and in accordance with regulations issued by the Secretary, for bona fide research purposes;

(20) Require that persons notify the Food and Drug Administration prior to the introduction of a drug into interstate commerce;

(21) Amend the current drug approval process by permitting a manufacturer, in lieu of submitting to FDA full reports (raw data) of safety and effectiveness studies, to submit either at the manufacturer's option or at the option of FDA a comprehensive summary of such data. Where a summary is submitted, FDA would have access to the full reports of safety and effectiveness data;

(22) Require an application for a drug approval to include at the time it is filed a releasable summary of data (excluding trade secret data). This summary would be available to the public and could be used by persons participating in the approval process;

(23) Require FDA to determine within 45 days of the date an application is filed whether it meets the requirements for filing. (If FDA makes no determination within the 45 day period, the application is deemed filed.) If FDA determines that the application does not meet such requirements, the applicant would be informed of FDA's reasons for such determination, including any determinations that may have been made by FDA regarding investigations and tests conducted by the applicant. Also, the applicant could request an informal hearing on the question of whether the application meets the requirements for filing;

(24) Require FDA to publish a notice in the Federal Register that an application has been filed and that the public may inspect portions of the applications that are not trade secrets. Thereafter, any person could submit written comments regarding the application;

(25) Require FDA within 30 days of the date on which an application is filed to make available the names of the reviewers. Also, to the extent possible, reviews of various portions of an application would be conducted concurrently;

(26) Require FDA, in the event it is determined that there are grounds for denying approval of an application, to publish a notice in the Federal Register and provide the applicant an opportunity for a hearing on the question of whether such application is approvable. Also, if the application has not been considered by an advisory committee during the approval process, the applicant would be entitled to review of the application by an advisory committee;

(27) Require FDA when approving or when denying approval of an application to set forth in writing a statement of reasons for FDA's action on the application;

(28) Require FDA during the approval process, to the extent possible and consistent with the efficient management of the review; not to change reviewers; to furnish the reviewers' findings to the applicant; to ensure that applications are distributed equitably (but not necessarily in equal numbers) among reviewers; and to take measures to ensure that reviews are conducted efficiently and expeditiously;

(29) Expand the factors considered by FDA in determining whether the methods used in, and the facilities and controls used for, the manufacture of a drug under review are adequate by adding as new factors a drug's stability and bioavailability;

(30) Establish new criteria by which FDA can immediately suspend approval of a drug found to present serious safety problems. Under present law, the Secretary of HEW may suspend approval only when he determines there is an imminent hazard to the public health. Under the bill, FDA could suspend approval if it is determined that the drug presents an unreasonable risk of illness or injury to any segment of the population. At present, the authority to suspend immediately approval of a drug is vested in the Secretary of HEW and may not be delegated. The bill permits the Secretary to delegate this authority to the Commissioner of Food and Drugs.

(31) Authorize FDA to establish an abbreviated approval procedure for generic versions of a drug that has been approved under the Act for at least 7 years and to approve generic drugs which meet appropriate pharmaceutical standards and are shown to be bioequivalent;

(32) Authorize FDA to revoke approval where a manufacturer fails substantially, and on a continuing basis, to comply with the new requirements relating to patient and physician labeling, drug promotion, prescription surveys, restrictions on distribution and dispensing, post-marketing surveillance, further scientific investigations, and batch certification;

(33) Amend the provisions of the Act relating to drug investigations to require, in addition to present requirements, that researchers inform research subjects of the benefits and risks associated with an investigational drug and obtain the subjects' informed, voluntary consent, in writing (other than where the drug is administered in an im-

minent life-threatening situation where there is insufficient time to obtain such consent). Researchers also would have to protect the health, rights, and privacy of research subjects and assure that the investigational drug is not promoted or advertised;

(34) Authorize FDA to establish new procedures relating to drug research investigations to expedite the early phases of drug research. Also, FDA would be required, in accordance with standards set out in the statute, to authorize institutions engaged primarily in health care research, teaching, or delivery to approve and supervise such drug research investigations;

(35) Permit a person who intends to investigate a drug to obtain advice from FDA regarding the investigational plan and other facets of the planned investigation;

(36) Require FDA to issue written guidelines regarding protocols and methods for conducting drug investigations;

(37) Establish an informal procedure for the resolution of scientific disputes between persons involved in drug research, and FDA;

(38) Require FDA to issue regulations that would permit an unapproved drug to be used to treat a small number of patients who have a serious disease, injury, or other health condition, for whom there is no adequate alternative form of therapy and who will not be subjected to an unreasonable risk of illness or injury. The statute would provide standards under which such approval would be authorized;

(39) Define two key terms used in the approval process: "safe" and "effective". These terms are not presently defined in the Act in the context of drug approval. "Safe" would be defined to mean that the health benefits of a drug outweigh its health risks. "Effective" would be defined to mean that a drug, when used in accordance with the conditions for use in its labeling, will have the effect it is represented in the labeling to have in the diagnosis, cure, mitigation, treatment, or prevention of a disease, injury, or other condition affecting health;

(40) Establish a "breakthrough" provision that would authorize FDA to approve for a period of three years, subject to various conditions, a drug that meets all criteria for full approval except that its effectiveness at the time it is submitted for approval is shown only by "significant evidence" and not by the higher standard of "substantial evidence" required for full approval. Before a drug could qualify for consideration as a breakthrough drug, the applicant would have to show that it is intended to be used to treat a condition that is life-threatening or severely debilitating or disabling in a significant portion of the patient population affected, that either there is no other method of treatment or the drug offers a major advantage in terms of safety or effectiveness, and that delay until the studies required for full approval are completed would cause significantly greater risks to patients affected by the disease than would approving the drug under the breakthrough provision;

(41) Exempt homeopathic compounds from the approval process unless FDA determines such compounds present a risk of illness or injury;

(42) Define the term "voluntary and informed consent" as used in the drug approval process and in the provisions relating to the imposition of post-approval requirements;

(43) Authorize four types of post-approval requirements: distribution and dispensing requirements, post-marketing surveillance, further scientific investigations, and batch certification. Before any such requirements could be imposed, FDA would be required to follow specified procedural steps, including referral of the matter to an advisory committee, and to determine that the grounds for imposing the requirement as spelled out in the bill exist. Once imposed, most post-approval requirements would automatically expire (subject to reinstatement in accordance with the standards and procedures for approval) at the end of a specified period of time;

(44) Authorize FDA to establish advisory committees to assist in making the determinations authorized under the Act;

(45) Grant FDA limited administrative subpoena authority;

(46) Authorize FDA to reimburse the attorneys fees, expert witness fees, and other costs of qualified persons who participate in proceedings under the Act;

(47) Permit the export, in certain circumstances, of unapproved drugs;

(48) Preempt State laws enacted subsequent to the enactment of the Bill regarding the packaging and labels of all drugs, and the labeling for non-prescription drugs, which impose requirements that are in addition to, or different from, comparable requirements under the Act. Upon application of a State, FDA must exempt a State requirement from preemption if FDA determines that such action would significantly enhance the public health within the State and would not impose an undue burden on interstate commerce;

(49) Provide that certain drugs that had been "grandfathered" under earlier Federal drugs laws would be deemed approved and thereby subject to the regulatory controls imposed under the Act for approved drugs;

(50) Establish a National Center for Drug Science to conduct and support drug research and training;

(51) Establish the Food and Drug Administration as a statutory agency within the Department of Health, Education, and Welfare, and provide that the Commissioner of Food and Drugs would be appointed by the President, by and with the advice and consent of the Senate; and

(52) Establish new conflict of interest provisions for persons working with FDA as consultants.

○


A11600 772165