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REPORT TO THE SUBCOMMITTEE ON
REORGANIZATION, RESEARCH AND
INTERNATIONAL ORGANIZATIONS
COMMITTEE ON GOVERNMENT
OPERATIONS
UNITED STATES SENATE



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Supervision Over Investigational
Use Of Selected Drugs B-164031(2)

Food and Drug Administration
Department of Health, Education,
and Welfare

BY THE COMPTROLLER GENERAL
OF THE UNITED STATES

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JULY 23, 1973



COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

The Honorable Abraham A. Ribicoff
Chairman, Subcommittee on
Reorganization, Research and
International Organizations
Committee on Government Operations 1508
United States Senate

Dear Mr. Chairman:

Pursuant to your request of October 20, 1971, and discussions with your office, this is our report on the investigational use of selected drugs as supervised by the Food and Drug Administration, Department of Health, Education, and Welfare.

As agreed with your office, we obtained formal written comments from the Department on matters in the report. Similarly, we obtained comments from the sponsors of drugs discussed in the report.

We plan no further distribution of this report unless you agree or publicly announce its contents.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "James B. Atchey".

Comptroller General
of the United States

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ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
HEW	Department of Health, Education, and Welfare
IND	investigational new drug
NAS/NRC	National Academy of Sciences/National Research Council
NIH	National Institutes of Health

COMPTROLLER GENERAL'S REPORT TO
THE SUBCOMMITTEE ON REORGANIZATION,
RESEARCH AND INTERNATIONAL
ORGANIZATIONS
COMMITTEE ON GOVERNMENT OPERATIONS
UNITED STATES SENATE

SUPERVISION OVER INVESTIGATIONAL
USE OF SELECTED DRUGS

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and Welfare B-164031(2) 22

D I G E S T

WHY THE REVIEW WAS MADE

The Chairman, Subcommittee on Reorganization, Research and International Organizations, Senate Committee on Government Operations, asked GAO to examine the Food and Drug Administration's (FDA's) supervision over the investigational use of selected drugs.

As agreed, GAO reviewed FDA records for 13 drugs designated by the Chairman's office. Also, as agreed, GAO obtained formal written comments on the report from the Department of Health, Education, and Welfare (HEW). Comments from drug companies on drugs discussed in this report were also obtained.

Basic information

FDA administers the Federal Food, Drug, and Cosmetic Act (FD&C Act). (See p. 5.)

The FD&C Act requires that before a new drug may be introduced into interstate commerce it must be approved for safety and efficacy. Evidence concerning a drug's safety and efficacy is obtained, in part, from clinical (human) tests conducted by the sponsor (manufacturer or others seeking to distribute the drug in interstate commerce). (See p. 6.)

When clinical tests involve interstate shipment of an unapproved drug, FDA requires the sponsor to submit an investigational new drug

(IND) application to exempt the IND from the ban on interstate shipment of unapproved drugs. The IND application must include data which demonstrates that clinical tests can be undertaken with reasonable safety. (See pp. 6 to 8.)

Under procedures set forth in the Code of Federal Regulations, FDA can terminate the IND exemption and require the sponsor to recall unused supplies of the drug at any time. Conditions which could prompt this action include

- omission of material facts from the IND application,
- existence of substantial evidence that the drug is unsafe or ineffective for the purpose intended,
- failure to follow the IND plan for investigational use,
- failure to submit accurate reports to FDA, or
- failure to promptly investigate and report to FDA any newly found serious or potentially serious hazards. (See pp. 10 and 11.)

From June 1963, when sponsors were first required to submit IND applications, through fiscal year 1972, about 9,000 IND exemptions were granted. In fiscal year 1972, 982 exemptions were granted, and 3,617 exemptions were active at the end of the fiscal year. (See p. 11.)

FINDINGS AND CONCLUSIONS

Drugs in which major safety questions arose tested in humans

In 10 of 13 cases reviewed, FDA raised questions concerning the safety of testing the drugs in humans because

--data from preclinical animal tests, long-term animal tests, or early clinical tests indicated there were possibilities of major drug-related adverse effects in humans or

--the preclinical or early clinical tests were inadequate.

In 2 of the 10 cases FDA experienced no problems in stopping the clinical tests after the safety questions arose. In the other eight cases, FDA permitted sponsors to begin (one case) or continue (seven cases) clinical tests after initial safety questions arose.

In four of the eight cases a causal association between the adverse effect and the drug was subsequently established and clinical tests were stopped. According to FDA, the association was related to additional safety questions which arose during long-term animal tests and was not related to the initial safety question except in one case. About 2,057 people were exposed to these 4 drugs.

In the other four cases the safety questions have not been completely resolved. In two of these cases, after considerable delay, FDA persuaded the sponsors to stop the clinical tests until the questions were resolved. In the other two cases, the questions were substantially resolved and the tests continued. About 2,498 people were exposed to these drugs.

FDA said it allowed tests for the eight cases because in each case it believed the drug's possible benefits outweighed the risks associated with the safety questions. Subsequently, in six cases, tests were stopped, according to FDA, when the benefit-risk ratio was no longer considered favorable.

In total, about 4,555 people were exposed to the 8 drugs. However, due to inadequate information in FDA files, GAO could not determine in all cases how many patients received the drugs after the safety questions arose. (See p. 12.)

In one case, although the sponsor had been allowed to start clinical tests, 13 months later in March 1970 FDA recommended to the sponsor that tests be discontinued until preclinical tests had been performed which would justify clinical testing. The clinical tests continued and in April 1970 the sponsor reported finding thymic lymphosarcomas (malignant disorders of lymphoid tissue invading the adjacent thymus gland) in mice during long-term animal tests. Proportionately fewer control mice had these disorders. FDA again advised the sponsor to stop clinical tests until the carcinogenicity question was resolved. However, the sponsor did not stop the tests until FDA threatened to withdraw the IND exemption in August 1971--16 months later. This drug had been given to about 194 patients during the tests. (See pp. 20 to 22.)

FDA advised GAO that:

--Evaluating a drug's safety in clinical tests intimately involves the drug's proposed use and expected benefits. It has been and continues to be FDA's policy to evaluate INDs in terms of benefits versus risks (including serious

health questions raised during animal studies) involved in the drug's experimental use.

--The benefit-risk ratio is not a constant and factors such as the severity of the condition being treated or the availability of other treatment must be considered in evaluating the ratio.

--Since 1970 procedures have been implemented to effect timely review of and decisions regarding INDs. (See p. 31.)

Because the 13 cases reviewed, which were not randomly selected, span about 9 years during which about 9,000 IND exemptions were granted, GAO recognizes that the conditions involving these cases may not be representative of FDA's processing of past and present IND cases. In addition, FDA's evaluation of INDs, in large part, is based on medical judgments about which GAO has no opinion. However, GAO believes that in several cases reviewed, the FDA actions appear to have lacked timeliness or aggressiveness.

Although FDA policy is to evaluate INDs in terms of benefits versus risks, the IND files reviewed did not contain documentation showing benefit-risk evaluations to support FDA actions. Rather FDA officials often differed in their opinions regarding a drug's safety and benefits. In some cases, FDA wrote sponsors expressing concern over a drug's safety while permitting clinical tests to continue.

GAO believes serious safety questions concerning testing drugs in humans should be resolved before allowing clinical tests to begin or continue, unless a written determination is made that benefits out-

weigh risks of its experimental use. (See p. 32.)

Reporting information on major drug-related adverse effects was delayed

The Code of Federal Regulations requires sponsors to promptly investigate and report to FDA any findings suggesting significant hazards and to immediately report alarming findings. Violations of these requirements may be referred to the Department of Justice for prosecution under section 301 of the FD&C Act.

Information on major drug-related adverse effects encountered in long-term animal tests of three drugs reviewed was not reported on a timely basis to FDA. The time lag between discovering the effects and reporting them ranged from 40 days to 19 months. (See p. 33.)

GAO believes that to maintain the integrity of the IND process, all requirements placed on IND sponsors must be strictly observed. In addition, FDA should institute a program to insure IND sponsors' timely performance and reporting of animal studies to FDA. (See p. 36.)

Policy on patient followup needed

For those situations where clinical tests are discontinued because of major drug-related adverse effects, FDA has no formal policy on whether patient followup should be provided and no formal guidelines describing adequate followup. However, FDA officials said each division of its Bureau of Drugs has informal operating procedures which cover followup.

In April 1972 FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to perform a study which would include consideration of followup problems.

The NAS/NRC report was submitted to FDA in January 1973 and was under review as of March 1973.

According to FDA, the FD&C Act provides ample authority to require, as a condition to granting the IND exemption, a commitment from the sponsor to provide followup. FDA has required no such commitment.

When FDA has requested sponsors to provide followup, the requests were for such actions as informing patients of the major drug-related adverse effects, conducting physical examinations and tests, and advising patients of the need for continued examinations and tests. (See p. 37.)

In 6 cases about 2,781 patients were exposed to drugs which were later found to cause major drug-related adverse effects during animal studies. The effects were serious enough to stop clinical tests because it was determined that the drug's risks outweighed the benefits. In these instances FDA did not effectively insure that patients were provided satisfactory followup. (See p. 37.)

GAO believes FDA should establish, as soon as possible, (1) a formal policy stating that the sponsor should provide patient followup and (2) guidelines describing adequate followup. The policy and guidelines could be refined if warranted by FDA's evaluation of the

NAS/NRC study. (See p. 48.)

RECOMMENDATIONS

The Secretary of HEW should direct the Commissioner, FDA, to:

- Make a written determination that a drug's benefits outweigh the possible risks of its experimental use, before allowing clinical tests to begin or continue when serious safety questions concerning testing drugs in humans arise. (See p. 32.)
- Institute a program to insure IND sponsors' timely performance and reporting of animal studies to FDA and emphasize to sponsors the need to proceed with clinical investigations in accordance with the Code of Federal Regulations. (See p. 36.)
- Establish (1) a patient followup policy which requires a written commitment in the IND application from the sponsor to provide appropriate followup before an IND exemption is granted and (2) guidelines describing adequate performance and reporting requirements for followup. (See p. 48.)

AGENCY ACTIONS AND UNRESOLVED ISSUES

HEW concurred in GAO's recommendations and said it had initiated action to implement them. (See pp. 32, 36, and 48.)

CHAPTER 1

INTRODUCTION

On October 20, 1971, the Chairman, Subcommittee on Reorganization, Research and International Organizations,¹ Senate Committee on Government Operations, requested us to examine the Food and Drug Administration's (FDA's) supervision over the investigational use of selected drugs.

As agreed with the Chairman's office, we reviewed FDA case files for 13 drugs--specifically designated by the Chairman's office--and considered their being tested in animals and patient followup. The case files were for drugs being tested for safety and efficacy.

We interviewed FDA officials and reviewed applicable legislation and FDA's regulations, policies, and practices governing the investigational use of new drugs. Our review was performed at FDA headquarters in Rockville, Maryland.

FDA'S RESPONSIBILITY TO REGULATE DRUGS

FDA, Department of Health, Education, and Welfare (HEW), administers the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended (21 U.S.C. 301). The FD&C Act requires that sponsors (manufacturers or others seeking to distribute new drugs in interstate commerce) file applications with FDA and obtain its approval before introducing such products into interstate commerce.

The FD&C Act defines a new drug as:

"(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except

¹ Formerly the Subcommittee on Executive Reorganization and Government Research.

that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

"(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

In carrying out its responsibilities, FDA reviews three types of applications: (1) investigational new drug (IND) applications to clinically test new products, (2) new drug applications, including supplements, to demonstrate that new products are safe, effective, and ready for marketing, and (3) abbreviated new drug applications to demonstrate effectiveness for drugs that previously have been approved for safety.

IND applications

The so-called Kefauver-Harris Amendments to the FD&C Act in 1962 increased Federal regulatory authority over clinical testing of new drugs, to minimize hazards inherent in new drug development and to insure as far as possible a responsible concern for the safety of the subjects. The amendments also provided a firm basis for promotion of improved methods and evaluation of standards in investigating new drugs and required a demonstration of the substantial efficacy of a drug before marketing.

The FD&C Act requires that, before a new drug may be introduced into interstate commerce, FDA must approve the drug for both safety and efficacy. To satisfy FDA requirements for safety and efficacy, the sponsor of a new drug must, among other things, clinically test the drug under

closely controlled conditions. Because this may involve the interstate shipment of an unapproved drug to qualified experts, since June 1963, FDA has required the sponsor to submit an IND application to exempt the IND from the ban on interstate shipment of unapproved drugs, thus permitting the interstate shipment of INDs for clinical studies.

Under FDA procedures promulgated on August 14, 1970, the sponsor, after submitting an IND application, must wait 30 days before beginning clinical tests. This delay is to enable FDA to review the application to make certain it contains the necessary information and to insure that patients are not exposed to unwarranted risks. The sponsor may initiate clinical testing 30 days after FDA has received its application unless in the meantime FDA has requested it to hold up. The 30-day period may be extended if FDA feels additional time is needed for the sponsor to correct deficiencies in the application. FDA also may waive the 30-day requirement if it believes such action is justified.

Before August 14, 1970, if a sponsor had submitted an IND application, the sponsor was free, with certain exceptions, to immediately proceed with the clinical investigation unless FDA presented an objection.

FDA requires the sponsor to submit, as part of the application, a report of the results of preclinical tests, usually on animals, from which the sponsor has concluded that clinical tests can be conducted with reasonable safety. Unless FDA raises questions concerning the sufficiency of the data to justify clinical testing, such testing may begin.

FDA's regulations (21 CFR 130) governing new drugs state, among other things, that the IND application must contain:

1. A statement covering all information available to the sponsor derived from preclinical investigations on animals and from any clinical studies and experience with the drug.
2. The name of each investigator and a summary of his experience and training which the sponsor considers appropriate to qualify the investigator as a suitable expert to investigate the drug.

3. An outline of any phase or phases of the planned investigations.

In addition, the regulations state that, for an IND application to be approved, the sponsor must agree to submit to FDA:

1. Accurate progress reports at reasonable intervals, not exceeding 1 year, of investigations and significant findings together with any significant changes in the information submitted to investigators.
2. Reports of any findings concerning the drug that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of its use. If the finding is alarming, it is to be reported immediately and the clinical investigations discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed.
3. A full report of the reason for discontinuing the investigations if facts show there is substantial doubt that they may be continued safely in relation to the drug's potential benefits.

The sponsor generally performs both preclinical animal tests, lasting at least 2 weeks, and long-term animal tests, lasting generally from 1 to several years. The long-term animal tests, which are allowed to be conducted concurrently with clinical tests, are designed to show the drug's long-term effects.

According to FDA, the length of preclinical animal tests needed before FDA allows clinical tests depends upon the type of drug being investigated, how long it will be given to humans, and the particular phase(s) in which the drug will be tested as defined in the IND application. The preclinical animal tests must be completed before clinical tests begin so that FDA can evaluate the results to insure that human subjects will not be exposed to unnecessary risks. If FDA believes the preclinical animal tests are not adequate to support clinical tests, it may refuse to grant an IND exemption.

FDA informed us that, in the initial stages of a drug's evaluation for safety, there is usually an interrelationship between studies in man and animals. As clinical tests progress, additional animal data is developed to support broader clinical tests and, ultimately, to support the general availability of the drug to the medical community.

The IND procedures for testing in humans are divided into three phases.

- Phase 1 covers the first trial in humans to determine pharmacological actions, such as human toxicity, metabolism, absorption, and elimination; the preferred route of administration and safe dosage range are also determined. The number of humans used in phase 1 varies but generally ranges from 20 to 50.
- Phase 2 covers the pharmacological actions in a larger number of patients, generally no more than 100 to 200, to prevent or control a specific disease.
- Phase 3 covers expanded trials on patients which provide a basis for assessing the drug's safety and efficacy and optimum dosage schedules in diagnosis, treatment, or prophylaxis.

FDA's Bureau of Drugs reviews IND applications. IND applications are screened by the Bureau's Office of Scientific Evaluation and assigned to one of the Bureau's six divisions for detailed analyses. The Consumer Safety Officer (a special administrative individual, not a medical doctor) within the applicable division reviews the file for completeness and correctness of form. This generally takes about 24 hours from the time the application is received. If the application is incomplete, it is rejected and a letter is sent to the sponsor informing it of the need for additional information and advising it not to start clinical studies.

If the IND application is complete, a copy is forwarded to the division's chief medical officer, chief chemist, and chief pharmacologist, who assign the application for analysis to a medical officer, a chemist, and a pharmacologist. In all cases the three disciplines analyze the application.

The analyses are forwarded to the chief medical officer (or in some cases, the medical officer assigned to the application) who consolidates the comments and decides whether to recommend to the applicable division director the acknowledgment or nonacceptance of the application. When the division director and his staff have reached a decision, FDA sends a letter of acknowledgment or nonacceptance to the sponsor.

Once an application has been acknowledged, the FDA staff assigned to it must periodically review the IND file within their respective disciplines, including all new data submitted, and prepare drug analysis reports.

FDA can terminate the exemption and require the sponsor to recall unused supplies of the drug at any time pursuant to procedures set forth in 21 CFR 130.3(d), if the Commissioner, FDA, finds that:

"(1) The submitted 'Notice of claimed investigational exemption for a new drug' contains an untrue statement of a material fact or omits material information required by said notice; or"

* * * * *

"(3) There is substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use; or

"(4) There is convincing evidence that the drug is ineffective for the purposes for which it is offered for investigational use; or"

* * * * *

"(7) The clinical investigations are not being conducted in accordance with the plan submitted in the 'Notice of claimed investigational exemption for a new drug'; or"

* * * * *

- "(10) The sponsor fails to submit accurate reports of the progress of the investigations with significant findings at intervals not exceeding 1 year; or
- "(11) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side-effects and precautions pertinent to the safety of the new drug * * *."

From June 1963, when sponsors were first required to submit IND applications, through fiscal year 1972, about 9,000 IND exemptions were granted. In fiscal year 1972 alone, 982 exemptions were granted and 3,617 exemptions were active at the end of the fiscal year.

CHAPTER 2

DRUGS IN WHICH MAJOR SAFETY

QUESTIONS AROSE TESTED IN HUMANS

In 10 of 13 cases reviewed, FDA raised questions concerning the safety of testing the drugs in humans because (1) data from preclinical animal tests, long-term animal tests, or early clinical tests indicated there were possibilities of major drug-related adverse effects in humans or (2) the preclinical tests or the phase 1 clinical tests were inadequate.

In 2 of the 10 cases FDA had no problem stopping the clinical tests after the safety questions arose. In the other eight, however, FDA permitted sponsors to begin or continue clinical tests after initial safety questions arose.

In one of the eight cases, FDA knew of the adverse effect when the IND application was submitted. In three cases, additional safety questions arose during long-term animal tests. In these four cases a causal association between an adverse effect and the drug was established and clinical tests were stopped. According to FDA, the association was not related to the initial safety question except in one case. About 2,057 people were exposed to these 4 drugs.

In the other four cases the safety questions were not completely resolved. In two of these, after considerable delay, FDA persuaded the sponsors to stop the clinical tests until the questions were resolved. In the other two cases, the questions were substantially resolved and tests continued. About 2,498 people were exposed to these drugs.

FDA said it allowed clinical tests for the eight cases because in each case it believed the drug's possible benefits outweighed the risks associated with the safety questions. Subsequently, in six cases, clinical tests were stopped, according to FDA, when the benefit-risk ratio was no longer considered favorable.

In total, about 4,555 people were exposed to the 8 drugs. However, since information in FDA files was inadequate, we could not determine in all cases how many patients received the drugs after the safety questions arose.

The following table shows initial safety questions that arose and, for three drugs, the additional safety questions subsequently raised through long-term animal tests.

<u>IND</u>	<u>Initial safety questions FDA noted</u>	<u>Additional safety questions FDA noted (note a)</u>	<u>Date clinical tests stopped</u>
A	Cancerous thymic tumors (3-63)	Same	12-64
B	Hepatic cell damage in dogs (1-65)	Hepatic tumors in rats (8-69)	8-69
C	Fibrosis of kidneys in dogs (5-69)	Bladder cancer in in mice (4-70)	4-70
D	Growth of breast nodules-- benign (7-69)	Growth of breast nod- ules--malignant (12-69)	1-70
E	Chemical structure simi- lar to that of IND "A" and cancerous thymic tumors (12-69)		8-71
F	Chemical structure similar to that of IND "A" and inadequate phase 1 testing (7-71)		12-71
G	Central nervous system stimulation (11-66)	(b)	ongoing
H	Numerous problems (11-71)	(b)	ongoing

^aThese questions involved significant factors which in FDA's opinion caused the benefit-risk ratio to become unfavorable.

^bNo additional questions were noted; according to FDA, initial questions were substantially resolved.

DRUGS WITH CONFIRMED ADVERSE EFFECTS

The following information is from files for four INDs for which a causal association between a major adverse effect and the drug was noted and for which clinical tests were stopped.

IND "A"--FDA received an IND application for this drug in June 1963 and granted the exemption in July 1963. The drug was to be tested in treating severe angina pectoris (chest pains caused by diseased heart muscle) and cardiac arrhythmias (irregular heart beat). In March 1963 before exemptions were required, the sponsor notified FDA that the drug was being used in clinical tests and that it had induced thymic lymphosarcomas (cancerous tumors of the thymus gland) in mice. The sponsor advised FDA that all investigators had been informed of the adverse effect and that some stopped clinical studies while others continued them. By letter dated April 15, 1963, FDA informed the sponsor that it was concerned about the lymphosarcomas but pointed out that an appraisal of the drug's potential hazard could not be made without specific information on the drug's proposed clinical use.

The sponsor provided additional information when the IND application was formally submitted to FDA in June 1963. The FDA pharmacologist, after reviewing the additional information, expressed concern about the carcinogenic potential of the compound and believed it might be advisable to discourage the sponsor in proceeding with clinical tests.

In July 1963 FDA contacted one of the investigators, a clinical pharmacologist at the National Institutes of Health (NIH), HEW, to obtain his opinion on the drug's potential risk. According to FDA, he stated that, on first learning of the lymphosarcomas, NIH had wished to discontinue testing; however, on further consideration, NIH decided that the possible benefits outweighed the risks since the drug was being used only in patients with severe angina pectoris and arrhythmias. On May 12, 1964, the FDA medical officer, in his written review of the drug, concluded that clinical trials could continue.

In following up on the drug, FDA, in a letter dated October 26, 1964, asked the sponsor to supply additional information on this drug's carcinogenic potential. The sponsor stated in a letter to FDA dated December 11, 1964, that all clinical tests were being terminated and provided FDA a copy of a comprehensive report--which was sent to clinical investigators in July 1963--covering a number of preclinical animal toxicity studies conducted with the drug.

The FDA medical officer noted that, according to the comprehensive report, there was an association between the administration of this drug to mice and the appearance of thymic (thymus gland) tumors in mice. The drug had been given to about 91 patients during the clinical tests.

FDA informed us it knew of the thymic lymphosarcoma findings before the IND application was filed. FDA explained that, because the clinical investigators were fully informed of the animal findings and human trials were to exclude children and were to be of limited duration where the usual life expectancies of the patients were less than 5 years, it concluded that the drug's potential benefits outweighed the known risks. Therefore, clinical tests were allowed to continue.

IND "B"--FDA granted an IND exemption for this drug in September 1964. Clinical tests were to be on treating emotional illnesses, bronchospastic disease, and migraine and carcinoid syndrome (a yellow circumscribed tumor in the small intestine, appendix, stomach, or colon).

In January 1965 FDA officials evaluated data included with the IND submission and noted that the sponsor's toxicological tests showed that dogs which had received this drug suffered hepatic (liver) cell damage.

The FDA medical officer in his written review of the drug in January 1965 noted that the damage was caused by administering moderate to high doses of the drug and was apparently reversible in two-thirds of the dogs when use of the drug ceased. FDA requested the sponsor to perform additional animal tests, including liver function tests. FDA did not advise the sponsor to discontinue the clinical tests but recommended that it limit the dosage and monitor liver functions closely. At a conference in April 1965, the sponsor agreed to comply with FDA's request and in July 1965 submitted additional toxicologic data.

The FDA medical officer, in his written review of the IND file in March 1967, stated that information being supplied to FDA was not specific enough and that little raw data has been submitted. After the medical officer's review, FDA, by letter dated April 3, 1967, recommended to the sponsor that clinical tests be held at phase 2 until the sponsor

(1) took measures to determine the cause of hepatic cell damage in test animals, (2) changed protocols for clinical tests to be more specific regarding aims, laboratory tests to be performed, and clinical evaluations to be made, and (3) provided other specific information. By letter dated July 14, 1967, the sponsor agreed to hold testing at phase 2 and provided the other information requested.

The FDA medical officer reviewed the IND file again in June 1968 and, pursuant to his recommendations, FDA by letter dated July 12, 1968, again requested additional animal tests because of hepatic findings, and recommended that, until these tests were completed, the use of the drug be limited to meaningful phase 1 studies and to potentially lethal entities--such as carcinoid syndrome. More information on the clinical tests was also requested. In August 1968 the sponsor agreed to limit the clinical tests and to perform additional animal toxicity studies.

In September 1968 the FDA medical officer's review of the IND file disclosed that tests on two patients detected abnormal liver functions. In October 1968 the medical officer noted that the drug had been studied in 126 patients, of which 118 had been given liver function tests. Abnormal liver function was reported in seven cases, two of which were of clinical significance but did not appear drug related.

In December 1968 the medical officer recommended that, before entering phase 3 clinical tests, metabolic studies in man and chronic toxicity studies be undertaken because of the hepatic problems. In February 1969 the sponsor submitted data on human metabolic studies and noted that sub-acute toxicity studies in primates had been started.

In August 1969 the sponsor informed FDA that the IND tests were being discontinued because hepatic tumors were found in rats during the long-term animal test. During the clinical tests, about 324 patients had been given the drug.

FDA said clinical tests were not discontinued upon finding the hepatic cell damage in dogs because

--the dogs were given high doses of the drug and one purpose of this was to elicit adverse effects,

--the effects were apparently reversible when use of the drug ceased,

--monitoring of liver function in humans showed no significant evidence of drug-related liver dysfunction.

FDA further stated that rat studies showed an entirely different type of drug-related adverse effect (liver tumors). When the sponsor learned of these findings, it immediately discontinued clinical studies.

According to the sponsor, hepatic tumors in rats were found following the 59th week of the long-term high and intermediate dose animal tests. Regarding the clinical tests, the sponsor advised us that the drug was administered to humans, with few exceptions, for no more than 3 months, and all dosage levels on a dosage-weight basis were significantly below those administered to the animals showing tumors.

IND "C"--FDA granted an IND exemption for this drug in September 1968. It was to be tested as a diuretic (to promote urination) in treating edema (abnormally large amounts of fluid in the body).

The FDA medical officer, in his written review of the IND application in May 1969, noted that data submitted with the IND application showed that kidney fibrosis developed in dogs given the drug and stated that, because of the drug's low safety margin in the preclinical dog tests, additional preclinical tests were needed and phase 2 tests should be delayed. In June 1969 FDA wrote to the sponsor pointing out the deficiencies the medical officer noted and stating that there was not adequate data to conclude that a sufficient safety margin existed for phase 2 testing. FDA did not explicitly forbid the phase 2 tests, and the sponsor proceeded with them.

The sponsor advised us that, in response to the June letter, it submitted amendments to the IND application in June and July 1969 which it believed appropriately dealt with the medical officer's reservations. However, the medical officer's subsequent written reviews in September and November 1969 stated that the sponsor had not fully resolved all the deficiencies FDA noted regarding the IND submission and all clinical tests should be discontinued until adequate animal tests were completed and analyzed.

In October 1969 an FDA pharmacologist's written review of the IND file stated that more data should be obtained from animal tests and acute toxicity studies should be performed in two more species, one a nonrodent. The review further stated that, because of the apparent low safety margin between the toxic dose in animals and the proposed human dose, the clinical use of the drug was a medical decision.

Because of the medical officer's and pharmacologist's reviews, FDA informed the sponsor, by letter dated January 6, 1970, of the low safety margin in the clinical tests and requested a reply indicating its intention to limit the tests or else a recommendation for termination of the IND exemption would be made to the FDA Commissioner.

By letter dated January 22, 1970, the sponsor responded to FDA's January 6 letter and informed FDA that it had suspended phase 2 tests. The sponsor indicated, however, that phase 1 tests were being continued, and FDA acknowledged in a letter dated January 30, 1970, that this was appropriate.

On April 27, 1970, the sponsor informed FDA that drug-related bladder cancer had been noted in rats and that all clinical tests had been discontinued. About 142 patients had been given this drug during clinical tests.

FDA informed us that the medical officer's May 1969 recommendation to delay phase 2 tests was based on findings of kidney fibrosis in dogs during subacute toxicity studies. Thereupon, FDA proposed that testing of the drug be limited to phase 1 studies to determine the drug's disposition and the degree of relevance of the animal findings. The sponsor's studies, according to FDA, showed that the toxicity shown in dogs was not unlike that produced by marketed potent diuretics.

FDA told us that finding bladder cancer in the long-term rat studies was not an issue when the kidney fibrosis in dogs was noted. In April 1970, when the sponsor discovered cancer in rats, it notified FDA and clinical investigators that clinical tests were to be discontinued. According to FDA, the type of toxicity shown in the rat studies was not directly related to that shown in the dog studies.

IND "D"--FDA granted an IND exemption for this oral contraceptive in January 1967. The IND file indicates that the sponsor was conducting tests with three different formulations of the drug.

A summary of animal test results dated December 18, 1967, showed the drug to be relatively nontoxic in mice and rats. The sponsor said additional studies were undertaken in monkeys and dogs and all findings in the primate studies were essentially normal. However, by letter dated July 11, 1969, the sponsor notified FDA that a breast nodule was found in May 1969 in a dog receiving the drug during a long-term test and that the same dog had six additional nodules in June 1969.

On July 15, 1969, FDA informed the sponsor that, because of the nodule finding, no additional patients should be included in any clinical tests. However, the sponsor requested that it be allowed to delay any action on its clinical tests until a biopsy was done on one of the nodules. FDA agreed.

On July 23, 1969, the sponsor informed FDA that according to the biopsy, the nodule was benign. The sponsor also informed FDA that the clinical tests were not then geared to adding large numbers of patients. FDA informed the sponsor that clinical tests did not have to be limited if the nodule was benign.

In December 1969 the sponsor notified FDA that 16 of 48 dogs in the long-term test had developed breast nodules. Seven of them had been biopsied--four were benign and three were mixed nodules with areas of premalignant change. About this time 1,500 to 2,000 women were receiving the oral contraceptive. Because of the adverse animal findings, FDA in January 1970 requested the sponsor to discontinue all clinical tests, except one which was 80 percent completed on 20 patients and had 2 to 4 weeks to run. The sponsor immediately complied.

The sponsor and FDA continually corresponded about the nodule findings. FDA explained that, after the initial nodule findings were known to be significant, appropriate action was taken in that all investigators were notified of the findings, clinical trials were discontinued (except for the single limited trial which was 80 percent completed), and a patient followup plan was presented to the sponsor.

CASES IN WHICH POSSIBLE
ADVERSE EFFECTS NOT CONFIRMED

For two drugs the possibility of major drug-related adverse effects was noted but not confirmed. In these cases the sponsors were reluctant to discontinue clinical tests. However, after a considerable delay, FDA persuaded them to discontinue the tests until the safety questions were resolved.

In the case of two other drugs, there has been disagreement within FDA and between FDA and sponsors on the possibility of major drug-related adverse effects and the safety of the drugs. In these cases FDA has allowed the sponsors to continue clinical tests. Information on these four cases follows.

Drugs suspected of carcinogenesis

IND "E"--FDA granted an IND exemption for this drug in February 1969. It was to be tested in treating angina pectoris and arrhythmia.

The FDA chemist, in his initial written review of the IND application in May 1969, concluded that the IND was passable from the standpoint of manufacturing controls for phases 1 and 2 clinical tests. The FDA pharmacologist, in his initial written review of the IND application in September 1969, noted small impurities in the drug, which in his opinion did not present any safety problems. This opinion was based on animal studies which had been performed with both the pure and impure drug. The pharmacologist also noted that this drug was structurally similar to other drugs, including IND "A."
(See p. 14.)

The medical officer, in his written review of the IND submission in December 1969, pointed out that preclinical tests were not adequate to support clinical tests, especially because most of the animal tests were performed with a drug containing 4-percent impurities. The medical officer recommended that the sponsor discontinue all clinical tests until adequate animal tests were performed. However, the FDA chemist and pharmacologist did not agree that clinical tests should be discontinued.

After considering the views of the medical officer, chemist, and pharmacologist, FDA, in March 1970, notified the sponsor of the medical officer's comments and requested responses. FDA also recommended that clinical tests be discontinued until chemistry and animal test results justified tests in humans. A March 1970 addendum to the medical officers' written review showed that the sponsor was proceeding with clinical tests.

In a conference on April 8, 1970, FDA again advised the sponsor to discontinue clinical tests, but the sponsor continued them. Also on April 8, but after the conference, the sponsor submitted study results to FDA which showed that thymic lymphosarcomas developed in some mice given the drug for 18 months in a chronic toxicity study. Control mice not given the drug also had these disorders. However, proportionately more mice given the drug developed tumors than control mice.

According to the sponsor, the incidence of all tumors fell within the expected spontaneous incidence for this strain of mice and there was no significant difference in the findings between the control and treated mice.

In January 1971 FDA discussed with the sponsor the significance of the mice study, again advising it to discontinue all clinical tests and asking it to provide a plan for long-term patient followup.

The sponsor replied on March 4, 1971, that (1) the clinical tests would continue, (2) it would not notify clinical investigators of the thymic lymphosarcomas in mice, and (3) it believed that a long-term followup plan was not necessary.

Subsequently, on March 19, 1971, the sponsor conferred with FDA and submitted data to support its position that the incidence of thymic lymphosarcomas seen in the mice study was not significantly different from the spontaneous incidence in control mice of the same strain. Data was also presented on the chemistry and metabolic properties of this drug in comparison with IND "A." In the sponsor's opinion, the data showed that this drug and IND "A" were very different in their chemistry and

metabolic properties and there was no scientific basis for considering the two compounds related insofar as any potential for carcinogenesis in mice was concerned. FDA told the sponsor that it could not reach any new conclusion until it reviewed the data submitted.

On June 15, 1971, FDA wrote the sponsor that its data did not satisfactorily answer the drug's carcinogenicity question. FDA again advised the sponsor to discontinue clinical tests.

FDA and the sponsor met in July 1971. The sponsor reiterated its position that clinical tests should continue and submitted additional data on the mice study to support its contentions. The sponsor agreed not to expand the current tests or start new tests until FDA reviewed all the data.

In August 1971 FDA, after reviewing the mice study in detail, advised the sponsor that FDA's review showed that the incidence of sarcomas was greater in mice given the drug than in control mice and that the compound's carcinogenicity question was, therefore, not yet resolved. FDA advised the sponsor to discontinue all clinical tests, threatening withdrawal of the IND exemption.

On August 27, 1971, the sponsor informed FDA that, although it believed that, on the basis of available evidence, it was reasonably safe to continue clinical tests, all such tests would be discontinued until the carcinogenicity question was resolved. As of November 17, 1972, the IND exemption remained in effect but clinical tests were discontinued. However, FDA has permitted emergency shipments of the drug for certain patients. During clinical tests it was given to about 194 patients.

FDA said the initial safety questions raised in December 1969, which were the basis for the March 1970 recommendation to discontinue clinical tests, were unrelated to the thymic lymphosarcoma questions raised in January 1971.

IND "F"--FDA granted an IND exemption for this drug in December 1969. It was to be used intravenously to treat angina pectoris and arrhythmias.

The sponsor submitted a supplement to the IND application in May 1970, which provided for a tablet form to be administered orally in further clinical tests. FDA informed the sponsor on June 3, 1970, that for administrative reasons the supplement was being regarded as a new and separate IND application.

The FDA pharmacologist, in his May 1970 report on IND "F," noted that the drug's chemical structure was closely related to that of a marketed drug which was not known to produce tumors in animals and that no data had been submitted with IND "F" which suggested possible tumorigenic effects.

However, he noted that the chemical structure of IND "F" was similar to that of IND "A," which was known to produce tumors in animals, and he therefore suggested that studies to evaluate any possible tumorigenic effect be strongly considered. The pharmacologist suggested that clinical tests using the drug intravenously be discontinued until an intravenous subacute toxicity test in another animal species at three dosage levels was conducted.

The FDA medical officer, in his written review of IND "F," also dated May 1970, stated that well-controlled phase 1 tests should be made before further extending phases 2 and 3 tests. In June 1970 the medical officer, in his written review of the supplement to IND "F," noted that some of the proposed tests would be somewhat premature because adequate and thorough phase 1 tests had not been performed.

FDA notified the sponsor of the matters brought up in its reviews of IND "F" and the supplement by letters dated September 14 and December 9, 1970, respectively.

The sponsor's replies in November 1970 and January 1971 did not clear up all the questions. In a letter to the sponsor dated March 19, 1971, FDA, in discussing both IND "F" and the supplement, stated that more information was needed and that data from foreign tests was unacceptable as the sole supporting evidence of safety and efficacy. The drug was being marketed

outside the United States, and the sponsor's main support for the drug's safety and efficacy was based on foreign tests.

On July 16, 1971, FDA notified the sponsor that a similar drug caused tumors in mice and asked it to consider suspending clinical tests until carcinogenic studies were finished and evaluated. The sponsor replied on August 16, 1971, that, in view of the available carcinogenicity data, it would not suspend tests.

In December 1971 the sponsor, in response to further FDA requests in November and December 1971, agreed to suspend clinical tests until additional data was available from in-process and planned animal tests. As of November 17, 1972, clinical tests were not being conducted.

About 91 patients had been given this drug. FDA said this IND was limited to high-risk cardiac patients and the tests were to gain insight into the drug's benefit-risk ratio.

INDs "E" and "F" (commonly referred to as beta blockers¹) were being tested as a new means of treating various types of severe heart conditions. Though beta blockers have structural similarities, their properties vary, which enables them to produce different effects. For example, one beta blocker (IND "A") was a known producer of cancerous tumors in mice, but another, a marketed drug, was not known to produce tumors in animals.

FDA officials told us that safety and efficacy considerations of beta blockers, including INDs "E" and "F," were the subject of discussions of two FDA advisory committees.

¹Beta blockers are drugs which prevent the stimulation of beta adrenergic nerve endings in the heart. Such nerve endings accelerate heart rate, increase the force of the heart's contraction, and increase conduction of nerve impulses within the heart. Beta blockers are a new means to treat certain disease states, such as irregular heart-beat or heart pain.

An Advisory Committee on Drug Related Carcinogenesis met on October 7, 1971, and concluded, among other things, that

- data relating beta blockers to carcinogenicity merits concern,
- at least 2-year carcinogenicity studies in two separate animal species should be completed and assessed for all beta blockers before clinical tests may start,
- if a carcinogenic potential is shown in animal studies, its significance should be determined in light of the drug's proposed use in man, and
- sponsors should be required, as an added part of the commitments undertaken to obtain an IND exemption, to obligate themselves specifically to provide adequate followup on all patients for whatever term might prove appropriate in the event of untoward development.

According to FDA, committee members were experts in animal carcinogenicity studies. They were not, however, clinical cardiologists and, in FDA's opinion, could not adequately assess the benefit-risk ratio of testing beta blockers in humans.

Because the committee noted that data relating beta blockers to carcinogenicity merited concern, FDA called together a Cardiovascular and Renal Advisory Committee, consisting of clinical cardiologists, to comment on the benefit-risk ratio of testing beta blockers in humans.

The Cardiovascular and Renal Advisory Committee met on April 14, 1972, and concluded that short-term (30-day maximum) acute phase 2 clinical tests, on certain severe conditions, for efficacy should be approved for beta blockers. Such approval would be contingent upon starting recommended long-term carcinogenicity studies in animals as outlined by the Advisory Committee on Drug Related Carcinogenesis in its October 7, 1971, meeting.

Subsequently, by letter dated November 16, 1972, FDA informed sponsors of beta blockers that

- short-term (30-day maximum) phase 2 acute human efficacy studies incorporating metabolic investigation would be permitted with these drugs after appropriate consultation and approval by FDA and
- FDA approval for such tests depended, in part, upon the sponsor's written commitment and initiation of 2-year animal carcinogenicity studies in rats and mice.

Drugs with other safety problems

IND "G"--FDA granted an IND exemption for this drug in October 1965. It was to be used to treat angina pectoris and coronary artery disease.

Central nervous system stimulatory effects (restlessness, nervousness, insomnia, irritability, and incoordination) of the drug were first noted in the medical officer's review of October 12, 1966. He believed such effects warranted further investigation.

By letter dated November 8, 1966, FDA advised the sponsor that, until certain information had been submitted, only limited phases 1 and 2 studies using a small number of patients under well-controlled conditions would be permitted. In addition, the sponsor was asked whether it planned to do additional animal studies in cats and monkeys to investigate these effects.

The sponsor supplied the requested information on November 21, 1966, and explained that it did not plan to initiate any additional animal studies on the effects to the central nervous system. It felt they occurred only at the higher dosage levels and were not severe enough to warrant discontinuing the drug's use even temporarily. On the basis of the sponsor's information, FDA permitted clinical tests to continue.

In July 1967 the medical officer's written review of the drug again noted the central nervous system stimulation. He stated that FDA was still concerned with the unknown cause of these effects. The FDA medical officer concluded that, before expanding to phase 3 testing in a large number of patients, the sponsor should perform additional metabolic, human pharmacologic, and clinical tests in a small number of patients under well-controlled conditions.

By letter dated November 13, 1969, FDA outlined some of the deficiencies noted and requested the sponsor to carefully monitor the clinical tests for central nervous system effects. FDA also advised the sponsor that the drug's usefulness had not been established. Despite this and the need to further evaluate these effects, the sponsor was allowed to continue with phase 2 tests in patients with severe heart problems. FDA officials, in September and November 1969 and March 1970,

indicated their opinion that the sponsor had conducted some phase 3 tests. As of November 17, 1972, the drug had been given to about 513 patients and clinical tests classified as phase 2 were ongoing.

FDA officials said the drug's clinical usefulness and safety remain to be defined from the ongoing clinical tests. The significance in terms of incidence rather than severity of the central nervous system effects will be judged in the light of the benefits to be gained from the drug.

IND "H"--FDA granted an IND exemption for this drug in October 1968. It was to be tested as a serum-cholesterol-lowering agent, primarily in patients with cardiovascular (heart and blood vessel) disease.

In a November 1968 written review, the FDA pharmacologist stated that available animal data supported clinical tests of no more than 3 months' duration, unless the results of a chronic toxicity study in dogs and rats was supplied. Also, additional data would be needed if phase 3 tests were undertaken. The sponsor was notified of the pharmacologist's concerns and the need for additional data by telephone in December 1968. The sponsor supplied additional data and continued the clinical tests.

In August 1970 the medical officer, in his written review, noted that a change had been made in the drug's name and chemistry and that tests were in the early portion of phase 3.

As of December 6, 1971, deaths of 32 patients involved in the clinical tests had been reported to FDA. Of the 32 patients who died, 15 were receiving a placebo (sugar pill), 12 were receiving IND "H," and 5 were receiving an approved drug. The sponsor and FDA concluded that none of these deaths were drug related but resulted because the subjects were high-risk cardiovascular disease patients.

On November 19, 1971, a medical officer reviewed the IND file for information on the drug because a new IND application for a different use of the drug was submitted in August 1971. The medical officer's written summary noted, among other things, that:

1. The drug's chemistry was unsatisfactory.
2. Animal and in-vitro tests raised several serious questions concerning the drug's ability to combine with food and drugs in the gastrointestinal tract and prevent their absorption.
3. Clinical tests were started in phase 2 on sick humans without first doing phase 1 in normal humans to establish base-line metabolism.
4. The clinical brochure for investigators was grossly inadequate.
5. Individual case reports were grossly inadequate and lacked detail, particularly regarding the deaths reported.
6. The drug causes various adverse effects, including gastrointestinal symptoms, hematological changes, and death.

The medical officer concluded that all clinical tests should be discontinued until his comments were resolved.

On December 8, 1971, a meeting was held among Bureau of Drugs officials concerning the medical officer's comments. They decided to permit the phase 3 tests to continue, barring any new adverse information which would require a reevaluation of the situation. Subsequently Bureau officials reviewed the IND file. They advised us that, on the basis of these reviews, they felt the problems the medical officer raised were unfounded.

The drug had been given to between 1,700 and 1,800 patients, and phase 3 tests were continuing as of November 17, 1972.

In commenting to us in March 1973, the sponsor addressed each of the six points the medical officer raised and offered the following explanations.

1. Because the drug was an unusual type of drug for FDA chemical reviewers, conferences were held to discuss it. Except for minor details being resolved, FDA chemists who had reviewed the drug agreed that

manufacturing and control data for the drug were satisfactory.

2. Extensive animal and clinical tests have shown no serious questions concerning the drug's ability to combine with food and other drugs in the gastrointestinal tract, if the drug is taken as directed. Weak binding of some drugs and foods has been seen in vitro, but this does not hold in long-term animal studies.
3. Clinical tests were started in normal volunteers with above-normal serum cholesterol levels. In this way, combined phase 1 and phase 2 studies were conducted simultaneously to determine both safety and serum-cholesterol-lowering ability with an economy of use of human subjects. Since the drug is not absorbed from the intestinal tract and is excreted intact, it is not metabolized.
4. The sponsor considers the clinical brochure entirely adequate and truthful.
5. Individual case reports for patients on the drug are, in the main, adequate in fact and contain an immense amount of clinical details. The amount and quality of data gathered regarding the safety and efficacy of the drug are sufficiently encouraging that a new drug application is in preparation.
6. Adverse effects associated with the use of the drug are relatively infrequent and minor. A comparison of patients who received the drug with those given a placebo provided statistical evidence showing that the drug, rather than causing death, has a strong trend toward prolonging life.

FDA VIEWS

FDA advised us that:

- Evaluating a drug's safety in clinical tests intimately involves the drug's proposed use and expected benefits.
- It has been and continues to be FDA's policy to evaluate INDs in terms of benefits versus risks (including serious health questions raised during animal studies) of the drug's experimental use.
- The benefit-risk ratio is not a constant, and factors such as the severity of the condition being treated or the availability of other treatment must be considered in evaluating the ratio.

FDA informed us that since 1970 procedures have been implemented to effect timely review of and decisions regarding IND applications. These include:

1. Instituting the 30-day hold. (See p. 7.)
2. Holding biweekly meetings within the Bureau of Drugs to discuss significant questions of safety and efficacy of INDs and establishing project coordination staffs and group leaders for evaluating major drugs.
3. Delegating authority for terminating IND exemptions to the Bureau's Director to insure more timely attention to termination cases.
4. Making increased use of advisory committees to determine the benefit-risk ratio.
5. Undertaking a major study of the IND process for format reporting of data and data storage and retrieval.
6. Preparing clinical guidelines for 29 drug categories, to classify the types of studies that constitute meaningful phases 1, 2, and 3 tests. These guidelines have not been finalized for issuance, but sponsors have used them in several cases.

CONCLUSIONS

Because the 13 cases reviewed, which were not randomly selected, span 9 years during which 9,000 IND exemptions were granted, the conditions involving these cases may not be representative of FDA's processing of past or present IND cases. In addition, FDA's evaluation of INDs, in large part, is based on medical judgments about which we have no opinion. However, in several cases reviewed, FDA actions appear to have lacked timeliness and aggressiveness.

Although FDA policy is to evaluate INDs in terms of benefits versus risks, the IND records reviewed did not contain documentation showing benefit-risk evaluations to support FDA actions. Rather FDA officials often differed in their opinions regarding a drug's safety and benefits. Also, in some cases, FDA wrote sponsors expressing concern over a drug's safety while permitting clinical tests to continue.

Serious safety questions concerning testing drugs in humans should be resolved before allowing clinical tests to begin or continue, unless a written determination is made that the drug's benefits outweigh the risks of its experimental use.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that the Secretary, HEW, direct the Commissioner, FDA, to make a written determination that a drug's benefits outweigh the possible risks of its experimental use, before allowing clinical tests to begin or continue when serious safety questions concerning testing drugs in humans arise.

HEW concurred and advised us that scientific supervisors will be directed to make a written determination regarding the benefit/risk ratio in each case. HEW further pointed out that FDA has recently taken several major steps to strengthen the IND process. (See p. 31.)

CHAPTER 3

REPORTING INFORMATION ON MAJOR

DRUG-RELATED ADVERSE EFFECTS WAS DELAYED

The Code of Federal Regulations (21 CFR 130.3(a)(6)) requires that:

"The sponsor shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindications, side-effects, and precautions pertinent to the safety of the drug. If the finding is alarming it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed."

Violations of the reporting requirement may be referred to the Department of Justice for prosecution under section 301 of the FD&C Act. The criminal penalties for convicted violators are not more than 1 year in prison or a \$1,000 fine or both for the first offense and not more than 3 years or \$10,000 or both for second and subsequent convictions for each charge.

Information on major drug-related adverse effects found in long-term animal tests of three of the drugs was not reported on a timely basis to FDA. The time lag between discovering the effects and reporting them ranged from 40 days to 19 months.

In one case reporting was delayed about 8 months. According to FDA, the sponsor's usual practice of delaying microscopic analyses of tissues of animals involved in chronic toxicity studies delayed the reporting.

In another case the results of a chronic toxicity study, indicating the possibility of drug-related carcinogenicity in mice, were submitted to FDA 19 months after the study was completed. The study was conducted by a British firm which, according to FDA, delayed reporting the results formally to the sponsor, and shortly thereafter the results were submitted

to FDA. However, in investigating this case, FDA has reasons to suspect that the sponsor knew of the study results before obtaining them formally. FDA's investigation is continuing.

In the third case, in which there was a 40-day delay in reporting, FDA concluded that the sponsor did not comply with the reporting requirements. The matter was referred to Justice, but the case was not prosecuted because Justice did not feel such action was warranted.

Information concerning the reporting of adverse effects for the three INDs follows.

IND "C" (See p. 17.)--The rats in a chronic toxicity study were killed in August 1969. In March 1970, about 7 months later, microscopic analysis of tissues of animals included in the study, which showed drug-related bladder cancer, was initiated. In April 1970 the analysis was completed and the results reported to FDA.

FDA made inspection visits to the sponsor on June 29 and 30, August 4, and October 20, 1971, to ascertain whether there was an undue delay in the reporting of the data to FDA. FDA informed us it could not conclude from these visits that the sponsor had been derelict in prompt reporting of these findings.

FDA explained that the sponsor had been performing many drug studies simultaneously and that, under the sponsor's practices, tissues of animals involved in chronic toxicity studies were not microscopically analyzed until some time after the animals' deaths. Therefore, because of this delay, which FDA did not consider unusual, the diagnosis of bladder cancer was not made until all bladder tissue had been analyzed. Once the cancer had been detected, the adverse effects were reported to FDA.

IND "E" (See p. 20.)--A study conducted by a British drug firm which indicated the possibility of drug-related carcinogenicity in mice was completed in September 1968, 5 months before the original IND had been submitted. The report of this study was not submitted to FDA until April 8, 1970, more than 19 months after the study's completion.

In a February 18, 1971, memorandum to the Director, Division of Cardiopulmonary and Renal Drug Products, Bureau of Drugs, the medical officer in charge of this IND recommended that withholding important and significant toxicity data be considered a basis for initiating legal action against the sponsor. The possibility of such action was discussed within FDA, but Bureau officials decided in May 1971 that, on the basis of the information available to them, legal action was not warranted at that time. FDA, however, did undertake action in January 1972 to investigate the matter further.

FDA officials informed us that the sponsor claimed it did not receive the study results from the British firm until March 1970. FDA made inspection visits to the British firm on January 17, 18, and 19, 1972. During these visits, FDA told us, it confirmed that the sponsor did not receive the formal report on the mice studies until March 1970. The firm indicated that it had held the report until all chronic animal studies had been concluded.

However, FDA said its inspections turned up evidence that the firm and the sponsor had been in contact from April 1968 to April 1970 and it was hard not to conclude that the firm must have discussed its findings with the sponsor. Therefore FDA made inspection visits to the sponsor in July 1972. According to FDA officials, as of April 30, 1973, the inspection report was still under review.

IND "I"--FDA granted the IND exemption for this drug in May 1963. It was tested as an oral contraceptive in 453 women before clinical tests were stopped in January 1966. According to FDA files, the sponsor discovered on December 13, 1965, that the drug had caused carcinoma in situ (cancerous microscopic lesions) in the mammary glands of two dogs which had received it in high doses continuously for 1 year. The sponsor did not notify FDA of this finding until January 21, 1966. Meanwhile the sponsor consulted with experts in the area, notified clinical investigators of the finding, and requested that all clinical tests be terminated.

In keeping with the Code of Federal Regulations, FDA concluded that the sponsor should have immediately notified FDA of its findings and its plans to evaluate the results of the experiment.

The sponsor informed us it felt the regulations required it to promptly investigate and notify FDA of its findings following investigation. The sponsor believed it used due diligence and sound judgment in this case.

FDA referred this matter to Justice. Justice, according to FDA, concluded that no legal action should be taken because, at the time of the discovery, the causal relationship between the drug and cancer was questionable and the sponsor took positive action in consulting experts and informing the investigators of the finding.

CONCLUSION

To maintain the integrity of the IND process, all requirements placed on IND sponsors must be strictly observed. In addition, FDA should institute a program to insure IND sponsors' timely performance and reporting of animal studies to FDA. In this regard FDA should undertake a survey of industry practices to determine the need for specific additional guidelines or regulations. In particular, FDA might require that sponsors provide it with a plan of animal studies proposed, which would include detailed schedules of expected dates for completing various phases of the studies and reporting the findings to FDA.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that the Secretary, HEW, instruct the Commissioner, FDA, to (1) institute a program to insure IND sponsors' timely performance and reporting of animal studies to FDA and (2) emphasize to sponsors the need to proceed with clinical investigations in accordance with the Code of Federal Regulations.

HEW concurred and advised us that FDA is promptly undertaking a survey of industry practices to determine the need for specific additional guidelines or regulations.

CHAPTER 4

POLICY ON PATIENT FOLLOWUP NEEDED

For those situations where clinical tests are discontinued because of major drug-related adverse effects, FDA has no formal policy on whether patient followup should be provided and no formal guidelines describing adequate followup. However, FDA officials said each division of the Bureau of Drugs has informal operating policies which cover followup.

In April 1972 FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to perform a study which would include consideration of followup problems.

Bureau officials said HEW's Assistant General Counsel for Food, Drugs, and Environmental Health concluded that the FD&C Act provides ample authority to require, as a condition to granting the IND exemption, a commitment from the sponsors to provide followup. FDA has not been requiring such a commitment.

When FDA has requested sponsors to provide followup, the requests were for such actions as informing patients of the major drug-related adverse effects, conducting physical examinations and tests, and advising patients of the need for continued examinations and tests.

Clinical tests were stopped in six IND cases reviewed because of major drug-related adverse effects indicated by long-term animal tests. These effects were hepatic tumors, breast nodules (two cases), bladder cancer, toxic eye side effects, and thymic tumors.

In four of the cases FDA requested the sponsors to provide followup, but the followup provided was not satisfactory to FDA. In the fifth case, the sponsor did not provide any followup in response to FDA's request. In the sixth case FDA did not request followup until 6 years after the clinical tests were discontinued. In this instance the sponsor agreed with FDA's request to obtain any data on followup the investigators might have conducted. The six cases are discussed below.

IND "A" (See p. 14.)--In December 1964 the sponsor notified FDA that clinical tests were discontinued because

drug-related thymic tumors were found in mice. The drug had been given to about 91 patients. When tests were discontinued, FDA did not request followup.

In June 1971 the FDA medical officer responsible for a similar drug (see IND "E" on p. 20) reviewed the file for IND "A" because of the similar effects in animal tests--thymic lymphosarcomas--and concluded that, because of the adverse effect and since 6 years had passed, all patients who had received the drug should be examined. By letter dated June 15, 1971, FDA requested the sponsor to provide full details of followup procedures and data derived from the followup.

In July 1971 the sponsor agreed to contact the investigators and request any available followup data or previously unreported data. However, by letter dated July 22, 1971, the sponsor pointed out to FDA that, although it would make every reasonable effort to contact the clinical investigators, less than maximum response from the investigators was possible because (1) use of the IND was discontinued in December 1964 and the investigators, by regulation, would not have to maintain records after December 1966 and (2) several investigators might have changed locations and would be difficult to locate.

By letter dated April 5, 1972, the sponsor advised FDA that it had solicited followup data from 44 investigators. The 36 responses received indicated that 20 investigators had used the drug. The sponsor reported that, according to the investigators, in those cases where followup data was available, no drug-related adverse reactions or serious complications were reported.

FDA informed us that, when use of the IND was discontinued, no thought was given to requiring followup. Patients were all suffering from severe and life-threatening conditions and their life expectancies were limited.

FDA further informed us that any association between a chemical (the drug) and human carcinogenesis was known to be very slow in developing and usually affected only a very small segment of the population exposed to the chemical.

IND "B" (See p. 15.)--In August 1969 clinical tests were stopped because drug-related hepatic tumors were found in rats during the long-term animal testing. The drug had been given to about 324 patients. FDA notified the sponsor in August 1969 that followup should be initiated.

In October 1969 the sponsor informed FDA that it was not considering followup and, instead, was considering additional animal tests. FDA on several occasions again requested followup. Finally, in August 1970, the sponsor submitted followup data which FDA considered deficient. The sponsor and FDA met during September 1970 to discuss a followup plan.

In a letter dated November 30, 1970, the sponsor advised FDA that it wrote all its investigators requesting followup and supplied printed forms to be filled out for each patient. In a letter dated January 12, 1971, FDA advised the sponsor of deficiencies in the planned followup and recommended a prospective rather than a retrospective followup.

On January 25, 1972, FDA sent a letter asking the sponsor to confirm that the patients given the drugs would receive long-term followup, which should include a thorough medical evaluation every 9 to 12 months. On March 27, 1972, FDA repeated this request in another letter.

Because no responses to the January and March letters were received, FDA requested its field inspectors to visit the sponsor to determine what followup had been made. A June 1972 inspection revealed that the sponsor had taken no further steps than had been reported to FDA on November 30, 1970.

A sponsor official informed the inspectors that reports had been received from the investigators, but, for the most part, were of little or no value. The sponsor had tried to evaluate the data obtained but could determine nothing of value and did not submit the data to FDA.

The sponsor took no further steps to recontact the investigators to clarify the data or obtain data from non-reporting investigators. After the inspection the sponsor agreed to furnish FDA with data on the results of its followup requests.

By letter dated July 5, 1972, the sponsor informed FDA that it had received followup information on 110 of the 324 patients treated with the drug and that no drug-related medical findings had been reported. The sponsor stated that it would again write to all investigators to request additional followup data on exposed patients.

The medical officer, in his written review of the IND in August 1972, concluded that the followup being provided was inadequate, both qualitatively and quantitatively. As of November 17, 1972, no additional followup data had been received from the sponsor.

The sponsor informed us on March 29, 1973, that the duration of the drug's dosage was, with few exceptions, no more than 3 months and all dosage levels on a dosage-weight basis were significantly below those employed in the animals showing tumors. The sponsor stated, however, that followup was continuing.

IND "C" (See p. 17.)--In April 1970 all clinical tests were discontinued because drug-related bladder cancer was found in test animals. The drug had been given to about 142 patients. In May 1970 FDA requested the sponsor to provide patient followup.

Some followup was provided but in October 1970 FDA informed the sponsor that some aspects of the followup were inadequate. In particular FDA urged that all patients be given physical examinations. FDA and the sponsor differed in their opinions regarding physical examinations. In November 1970 FDA discussed with the sponsor the appropriateness of requiring cystoscopies (visual examination of the urinary tract) as part of the physical examination. Though FDA believed that cystoscopies should be performed, the sponsor believed pap smears of the urine (microscopic studies of urine specimens) would be adequate. However, in January 1971, FDA advised the sponsor that the physical examinations should include cystoscopies.

From April to June 1971 FDA consulted experts regarding the significance of finding drug-related bladder cancer in test animals and the appropriateness of the planned followup procedures.

By letter dated December 27, 1971, FDA again urged the sponsor to provide adequate followup. This letter pointed out that FDA had consulted several eminent urologists about a followup plan. The urologists recommended cystoscopies. FDA also pointed out that this was apparently somewhat in variance with recommendations by the sponsor's urologic consultants, who stressed that the main diagnostic reliance should be placed on periodic pap smears of the urine. Therefore, in this letter, FDA recommended the following.

- The sponsor or the clinical investigators were to ascertain that the patient was under expert urologic care.
- The sponsor was to supply all clinical investigators with a full resume of all animal studies dealing with the bladder cancer problem.
- The investigator and his consultant urologist were to determine the actual medical procedures to be performed on the patients.

By letter dated January 6, 1972, the sponsor indicated that it was undertaking a followup program in response to FDA's latest request. By letter dated February 2, 1972, the sponsor supplied FDA with information on animal data it was providing to the investigators requesting followup. As of November 17, 1972, FDA had received no additional information on the followup.

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FDA attempts to obtain adequate followup for INDs "B" and "C" are discussed in a Bureau of Drugs internal memorandum dated April 21, 1971, from the Director, Division of Cardiopulmonary and Renal Drug Products, to the Acting Director, Office of Scientific Evaluation. This memorandum stated:

"Each of the firms * * * were requested to perform adequate follow-up * * *. Initially, each of the firms had delayed initiation of any type of follow-up. Subsequently, each of the sponsors, under repeated prodding, had initiated follow-ups. However, in each case, the follow-up which the

firms have started are inadequate. In each case three deficits exist:

- "a. Failure to follow-up all subjects and patients who had received the experimental drug.
- "b. Failure to have subjects and patients suitably fully informed of the results of the animal study and its possible significance.
* * *
- "c. Failure to perform all studies requested with each subject and patient."

* * * * *

"It is of note that approximately 11 months * * * and 19 months * * * have elapsed since the sponsors were requested to perform clinical follow-ups."

FDA said the question of what constitutes appropriate followup was difficult to resolve in these cases. For IND "B" the exact type of followup that should be done was unknown from the scientific standpoint. For IND "C" FDA obtained recommendations on the type of followup which should be performed (including specific medical procedures to be followed) from outside urologists as well as scientists at the National Cancer Institute, NIH. The experts often disagreed as to what medical procedures should be performed, and the severity of some of the recommendations was cause for concern both within and without FDA.

IND "D" (See p. 19.)--In January 1970 clinical tests were discontinued because drug-related breast nodules were found in dogs, and FDA wrote the sponsor on January 28, 1970, that followup should be provided. The drug had been given to between 1,500 and 2,000 women.

On February 6, 1970, the sponsor acknowledged FDA's letter and stated that comments regarding followup would be furnished soon. Between March and June 1970 the sponsor and FDA corresponded regarding followup. During this period the sponsor requested a modification of FDA's request for followup. By letter dated June 29, 1970, FDA advised the

sponsor that it would further communicate with it regarding followup after FDA had further considered the matter. However, according to the sponsor, it had heard nothing further from FDA concerning followup until March 1972.

By letter dated March 28, 1972, FDA asked if the sponsor intended to do any followup. On April 13, 1972, the sponsor replied that, since it believed a followup program would not yield meaningful information, it had not initiated one.

In commenting to us, the sponsor supplied reasons why it felt followup would not be meaningful. The sponsor stated that numerous factors--such as intervening pregnancy or exposure to other medication, pollutants, or diseases--affecting the health of patients who participated in the clinical tests had occurred and could continue to occur. Also study design problems for a followup program arise because patients have received medication over varying periods of therapy and varying periods of discontinuance. Therefore, to obtain valid information about the incidence of subsequent disease, a suitably matched--both on a historical basis and for subsequent environmental exposure--control group would have to be established. The sponsor stated that this was not possible.

In addition, the sponsor informed us that, although some consider the occurrence of mammary nodules in dogs receiving IND "D" to have raised a safety question, it did not believe that any judgment could be made on the significance of this finding in women who had received the drug.

FDA informed us, in March 1973, that it now agreed that a followup program would not yield meaningful information since similar circumstances (see IND "I," below) had shown that patients get lost to followup rapidly or transfer to other oral contraceptives.

IND "I" (See p. 35.)--In January 1966 clinical studies were discontinued because drug-related carcinoma in the mammary glands of dogs receiving the drug was found. The sponsor willingly initiated a followup program. However, difficulty in followup was encountered due to patient relocation and lack of patient cooperation. Although the sponsor actively pursued a followup program, through 1971 only about one-third of the patients who had received the drug had been located and received followup examinations.

In June 1971 the sponsor advised FDA that the results of followup examinations and extensive human and animal data obtained since 1966 indicated that no relationship existed between the initial long-term animal studies and human experience. Also according to the sponsor, the likelihood of continued followup yielding solid data was weakened by the increasing possibility of disease occurring which could not be isolated as having an IND "I" origin and by the fact that many patients were placed on other oral contraceptives after clinical tests with IND "I" were discontinued. The sponsor stated that, as a result, followup would be continued only through 1971 and a final report would be submitted in 1972.

The final report, submitted in June 1972, showed that 134, or about one-third, of the 453 patients who had actually received the drug had been located and had been examined. No significant findings were reported, and the sponsor indicated that followup was being discontinued. As of November 17, 1972, the IND file contained no additional material on followup.

IND "J"--FDA granted an IND exemption for this drug in August 1967. It was to be used as a coronary vasodilator (an agent that dilates blood vessels) for treating angina pectoris and peripheral vascular disorders.

In September 1971 clinical studies were discontinued because drug-induced toxic eye side effects (cataracts) were found in dogs which had received the drugs for approximately 5 months in a chronic animal toxicity study. FDA requested the sponsor to provide followup. In November 1971 the sponsor suggested doing followup on a limited number of patients. FDA insisted that all patients be examined. In December 1971 the sponsor agreed with FDA.

The sponsor submitted status reports in December 1971; January, March, June, August, and December 1972; and January and March 1973 on followup eye examinations performed.

The August 1972 status report showed that 129, or about 46 percent, of the 283 patients who had received the drug had received followup eye examinations. Of the 129 patients examined, 54, or 42 percent, had some evidence of eye changes which could lead to cataracts. The report also showed that 42 patients in a control group who had not received the

drug also were given eye examinations in which it was found that 23, or 56 percent, had some cataract development. The control group was made up of subjects who had participated in the clinical tests of IND "J" but received only a placebo and of subjects who had not participated in the clinical tests but were selected as comparable to patients given IND "J." The latter group made up the majority of the control group.

The medical officer in his November 7, 1972, written review of IND "J," analyzed data in the August status report and concluded that "* * * in the absence of detailed information as to the sex, age and general health of the subjects, little or no approach can be made to estimate the significance of these data." Documents in the IND file indicate that as of November 1972 Bureau of Drugs officials considered the followup inadequate.

Subsequently a status report was submitted to FDA by letter dated December 22, 1972. It showed that 131, or about 46 percent of the 286 patients who had received the drug, had received followup eye examinations. Of the 131 patients examined, 63, or about 48 percent, had some evidence of cataract development. The report also showed that 52 patients in a control group also were given eye examinations in which it was found that 32, or 62 percent, had some cataract development.

The latest status report (March 1973) showed:

- 131, or about 48 percent, of the 271 patients who had received the drug had been given followup eye examinations. Of the 131 patients examined, 63, or about 48 percent, had some evidence of cataract development.
- Of 59 control group patients examined, 38, or 64 percent, had some cataract development. Among these, 17, or about 12.9 percent of the patients, and 8, or about 13.5 percent of the control group, showed a specific type of cataract development possibly related to concomitant drug administration or disease state.

The number of patients which were reported as having received the drug varied from 271 to 286 in the three status

reports, and the number of subjects examined in the control group increased from 42 to 59. For the 17 additional control subjects examined, 15 more were reported to have some cataract development. This considerably raised the ratio of controls having cataract development versus controls showing no sign of cataract development.

FDA officials informed us in March 1973 that in many cases patients were in an age group in which a high incidence of cataracts could be expected. Additionally many patients had not had eye examinations before being put on the drug. The FDA officials believed that the sponsor has made a creditable effort at followup.

FDA officials further said the experience with this IND indicates that all patients receiving any IND in phase 1 and initial phase 2 clinical tests should be given eye examinations before being administered the drug.

The sponsor and its ophthalmology consultants have concluded that none of these cataracts were related to IND "J," and as of March 1973 followup was continuing.

MORAL AND LEGAL CONSIDERATIONS
OF PATIENT FOLLOWUP

Bureau of Drugs officials and HEW's Assistant General Counsel for Food, Drugs, and Environmental Health discussed FDA's legal powers to require followup. Bureau officials told us in May 1972 that the Assistant General Counsel concluded that the FD&C Act provides ample authority to require followup under an IND because FDA could require, as a condition to granting an IND exemption, a commitment to follow up on patients should adverse effects suggest such a need. Presently FDA requires no such commitment.

According to Bureau officials, whether followup is medically necessary depends on the facts and the legal considerations on this question are minor when compared with the medical, ethical, and moral issues. They stated that some of the questions regarding such a requirement are as follows:

1. How should the information be conveyed to a patient when new data from clinical tests, animal tests, or other sources suggest a potential hazard previously unsuspected?
2. Should the possibility of these unexpected findings occurring and the ensuing followup be discussed in obtaining informed consent?¹
3. When this new hazard involves the possibility of tumors in animals and the significance is unknown in man, what should the patient be told?
4. How long should followup continue?

¹Informed consent, as defined in the Code of Federal Regulations, provides that the clinical investigator must inform any humans, or their representatives, to whom an IND is to be administered that such drug is being used for investigational purposes and obtain the consent of such humans or representatives. For phases 1 and 2 testing the consent must be written.

5. Should the responsibility for followup rest with the sponsor, the investigator, the Government, or the individual's physician?

In April 1972 FDA contracted with NAS/NRC to study the problem and develop possible answers to these questions. The NAS/NRC report was submitted to FDA in January 1973 and was under review as of March 1973.

CONCLUSIONS

In 6 cases about 2,781 patients were exposed to drugs which were later found during animal studies to cause major drug-related adverse effects serious enough to stop clinical tests. In these instances FDA was not effective in insuring that the patients were provided satisfactory followup.

Further, FDA is following a course which will not begin to provide future patients with protection until some time after the NAS/NRC study has been evaluated. Meanwhile persons exposed during tests to drugs which are found capable of causing major adverse effects will receive only that degree of followup which the sponsors will provide either voluntarily or through FDA persuasion.

FDA should establish, as soon as possible, (1) a formal policy stating that the sponsor should provide patient followup and (2) guidelines describing adequate followup. The policy and guidelines could be refined if warranted by FDA's evaluation of the NAS/NRC study.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary, HEW, instruct the Commissioner, FDA, to establish (1) a patient followup policy which requires a written commitment in the IND application from the sponsor to provide appropriate followup before an IND exemption is granted and (2) guidelines describing adequate performance and reporting requirements for followup.

HEW concurred and advised us that FDA is changing the IND forms to require such a written commitment and has made known its intention to do so in the lay and industry press. In addition, HEW informed us that FDA has implemented some of the recommendations in the NAS/NRC report, is continuing

to evaluate the report, and plans to issue appropriate guidelines regarding followup soon.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

JUN 21 1973

Mr. Morton A. Myers
Assistant Director
Manpower & Welfare Division
General Accounting Office
Washington, D.C. 20548

Dear Mr. Myers:

The Secretary has asked that I respond to your request for our comments on a draft of your report to the Chairman, Subcommittee on Executive Reorganization and Government Research, Committee on Government Operations, entitled, "Supervision Over Investigational Use of New Drugs." Our comments are enclosed.

We appreciate the opportunity afforded us to comment on this report in draft form.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "J. B. Cardwell".

James B. Cardwell
Assistant Secretary, Comptroller

Enclosure

APPENDIX I

COMMENTS OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ON THE REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES TO THE SUBCOMMITTEE ON EXECUTIVE REORGANIZATION AND GOVERNMENT RESEARCH, COMMITTEE ON GOVERNMENT OPERATIONS OF THE UNITED STATES SENATE ENTITLED, "SUPERVISION OVER INVESTIGATIONAL USE OF SELECTED DRUGS"

General

The recommendations and suggestions made in the report are pertinent and constructive. They accurately identify several aspects of the Investigational New Drug Application (IND) and New Drug Application (NDA) review process where the Food and Drug Administration is already implementing steps to improve procedures. However, one section of the report does deserve a note of clarification. There may be some confusion with respect to the discussion in Chapter 3 concerning the apparent delay of reporting information on the adverse effects of three drugs. We believe that the record is clear that, of the three drugs in which there was an apparent delay in the reporting of adverse effects, only in one case could it be documented that the sponsor did not comply with the IND reporting requirements. In this case, the Justice Department concluded that the evidence did not justify prosecution. In the second case, the results of the completed chronic toxicity studies were not available to the sponsor of the IND until very shortly before its submission. However, there was no evidence that a carcinogenic effect was demonstrated and, therefore, it could not be classified as an "alarming reaction" requiring immediate reporting. In the third case, the manufacturer's internal scheduling procedures were such that there was a delay in processing tissues, but the results were submitted in compliance with regulations.

Comments on specific recommendations are as follows:

GAO Recommendation:

The Secretary of HEW should direct the Commissioner, FDA, to make a specific written determination that the benefits to be derived from a drug outweigh the possible risk involved in its experimental use, before allowing clinical tests to begin or to continue when serious health questions concerning the safety and testing of drugs in humans arise.

BEST DOCUMENT AVAILABLE

Department Comment:

We concur. While a written record may not have been kept in all past cases, it has always been FDA policy to make such determinations on each and every drug. Now, however, scientific supervisors will be directed to make a written determination regarding benefit-to-risk ratio in each case.

GAO Recommendation:

The Secretary of HEW should direct the Commissioner, FDA, to institute a program to insure timely performance in reporting of animal studies by sponsors of drugs in investigational use and emphasize to sponsors the need to proceed with such investigations in accord with the Code of Federal Regulations.

Department Comment:

We concur in this recommendation. The Food and Drug Administration is promptly undertaking a survey of industry practices to determine the need for specific additional guidelines or regulations.

GAO Recommendation:

The Secretary of HEW should direct the Commissioner, FDA, to establish a policy governing patient follow-up which requires a written commitment in the IND application from the sponsor to provide appropriate follow-up before an IND exemption is granted.

Department Comment:

The Food and Drug Administration is in the process of changing the IND forms to require such a commitment and has previously made known its intention to do so in the lay and industry press.

GAO Recommendation:

The Secretary of HEW should direct the Commissioner, FDA, to establish guidelines describing adequate performance and reporting requirements for patient follow-up.

Department Comment:

We concur. As brought out by GAO in their report we contracted with the National Academy of Sciences to perform a study which

APPENDIX I

would include consideration of the problems associated with patient follow-up. We have received and are evaluating a report prepared on this study. FDA has already implemented some of the report's recommendations and plans to issue appropriate guidelines regarding patient follow-up in the near future.

In addition to the above specific actions, we believe it is important to point out several major steps that the Food and Drug Administration has recently taken to strengthen the IND/NDA process. They have included:

- ... a major study of the IND/NDA process for format; reporting of data; data storage and retrieval;

- ... the preparation of clinical guidelines for 29 categories of drugs;

- ... a program for an inspection of laboratories from which reports are being submitted for INDS.

FDA has also instituted a 30-day hold for the purposes of weighing the benefit-to-risk ratio in light of preclinical and other data supplied in the initial submission; the formulation of guidelines for appropriate patient follow-up where indicated from the standpoint of significant safety questions; and a major review of all aspects of preclinical studies by appropriate experts in pharmacology.

PRINCIPAL OFFICIALS OF THE
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
RESPONSIBLE FOR
THE ACTIVITIES DISCUSSED IN THIS REPORT

	<u>Tenure of office</u>	
	<u>From</u>	<u>To</u>
SECRETARY OF HEALTH, EDUCATION, AND WELFARE:		
Caspar W. Weinberger	Feb. 1973	Present
Frank C. Carlucci (acting)	Jan. 1973	Feb. 1973
Elliot L. Richardson	June 1970	Jan. 1973
Robert H. Finch	Jan. 1969	June 1970
Wilbur J. Cohen	Mar. 1968	Jan. 1969
John W. Gardner	Aug. 1965	Mar. 1968
Anthony J. Celebrezze	July 1962	Aug. 1965
ASSISTANT SECRETARY (HEALTH) (note a):		
Charles C. Edwards	Mar. 1973	Present
Richard L. Seggel (acting)	Dec. 1972	Mar. 1973
Merlin K. Duval	July 1971	Dec. 1972
Roger O. Egeberg	July 1969	July 1971
Philip R. Lee	Nov. 1965	Feb. 1969
COMMISSIONER, FOOD AND DRUG ADMINISTRATION:		
Sherwin Gardner (acting)	Mar. 1973	Present
Charles C. Edwards	Feb. 1970	Mar. 1973
Herbert L. Ley, Jr.	July 1968	Dec. 1969
James L. Goddard	Jan. 1966	June 1968
Winton B. Rankin (acting)	Dec. 1965	Jan. 1966
George P. Larrick	Aug. 1954	Dec. 1965

APPENDIX II

	<u>Tenure of office</u>	
	<u>From</u>	<u>To</u>
DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION (note b):		
J. Richard Crout (acting)	May 1973	Present
Henry E. Simmons	Apr. 1970	May 1973
John J. Jennings (acting)	May 1969	Apr. 1970
B. Harvey Minchew (acting)	July 1968	May 1969
Herbert L. Ley, Jr.	Sept. 1966	July 1968
Robert J. Robinson (acting)	Mar. 1966	Sept. 1966
Joseph H. Sadusk, Jr.	Apr. 1964	Mar. 1966
Ralph B. Smith (acting)	Aug. 1962	Apr. 1964

^aBefore November 1972 this position was designated as Assistant Secretary for Health and Scientific Affairs. In March 1968, the Assistant Secretary was given direct authority over the Public Health Service and FDA and the functions of the two organizations were re-aligned.

^bName changed to Bureau of Drugs as of February 1, 1970. Formerly called the Bureau of Medicine.