REPORT TO THE CONGRESS

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

Federal Control Of New Drug Testing Is Not Adequately Protecting Human Test Subjects And The Public

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

The Food and Drug Administration has neither adequately monitored new drug tests nor adequately enforced compliance with testing requirements. Consequently, it lacks assurance (1) that the thousands of human subjects used in such tests annually are protected from unnecessary hazards of new drugs or (2) that the test data used in deciding whether to approve new drugs for marketing is accurate and reliable.

HRD-76-96 JULY 15, 1976

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

B-164031(2)

To the President of the Senate and the
Speaker of the House of Representatives

This report shows that the Federal control over new drug testing is not adequately protecting human test subjects and the public. The Food and Drug Administration, Department of Health, Education, and Welfare, is responsible for administering the activities discussed in this report.

We made our review pursuant to the Budget and Accounting Act, 1921 (31 U.S.C. 53), and the Accounting and Auditing Act of 1950 (31 U.S.C. 67).

We are sending copies of this report to the Director, Office of Management and Budget; the Secretary of Health, Education, and Welfare; and the Secretary of Defense.

Comptroller General
of the United States

Contents

ABBREVIATIONS

DOD	Department of Defense
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
IRC	institutional review committee
NIH	National Institutes of Health

COMPTROLLER GENERAL'S
REPORT TO THE CONGRESS

FEDERAL CONTROL OF NEW DRUG TESTING IS NOT ADEQUATELY PROTECTING HUMAN TEST SUBJECTS AND THE PUBLIC

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

D I G E S T

The Food and Drug Administration is not adequately regulating new drug testing to insure that human test subjects are protected and that test data is accurate and reliable.

The 1962 amendments to the Federal Food, Drug, and Cosmetic Act and the Food and Drug Administration's regulations require the agency to closely control the clinical (human) testing of new drugs. The act requires that the agency approve a new drug for safety and efficacy before it is introduced into interstate commerce. (See p. 1.)

Since June 1963 the Food and Drug Administration has required sponsors--persons accepting responsibility for investigating new drugs--to submit investigational new drug applications to exempt unapproved new drugs from the ban on interstate shipment, thus permitting shipment to qualified experts (clinical investigators) for clinical studies to obtain evidence concerning safety and efficacy. (See pp. 1 to 3.)

Within the Food and Drug Administration, the Bureau of Biologics regulates the testing of biological drugs and the Bureau of Drugs regulates all other human drugs.

At June 30, 1974, there were about 4,600 active investigational new drugs involving about 250,000 test subjects. About 1,200 sponsors and 5,000 clinical investigators were under regulation by the Bureau of Drugs. About 200 sponsors and 4,400 clinical investigators were under regulation by the Bureau of Biologics. The clinical investigations under a single investigational new drug application may include several thousand human test subjects. (See pp. 3 to 6.)

AGENCY MONITORING EFFORTS

Poorly conducted clinical investigations unnecessarily expose human subjects to potential hazards and could result in the Food and Drug Administration's approving a drug for marketing on the basis of inaccurate and unreliable data. To prevent this, the agency must monitor the performance of clinical investigations. Such reviews, however, have been limited.

Before 1972 the agency's monitoring was limited to about 40 inspections of clinical investigators suspected of wrongdoing. From July 1972 through June 1974, the agency, in a special survey, inspected 15 sponsors and 155 of their clinical investigators. In 1974, at GAO's request, the agency inspected an additional 83 clinical investigators.

In most cases, clinical investigators were not fully complying with the laws or agency regulations and sponsors were not adequately monitoring their clinical investigators. (See pp. 8 to 21.)

ENFORCEMENT EFFORTS

The Federal Food, Drug, and Cosmetic Act and new drug regulations provide for administrative and legal actions against those who violate requirements. The Food and Drug Administration has made limited use of these enforcement actions. Since the 1962 amendments, four cases have been referred to the Department of Justice, which prosecuted two clinical investigators for submitting fraudulent data. Administrative sanctions have not been effectively used. (See pp. 21 to 25.)

INFORMED CONSENT

The Federal Food, Drug, and Cosmetic Act explicitly requires that human beings participating in an experiment with a new drug be informed of such use and that their consent, or that of their representative, be obtained. New drug regulations contain

detailed requirements concerning how such informed consent should be obtained.

Of 238 Food and Drug Administration inspections made since 1972, consent information was available on 172 clinical investigators and 52 sponsor/investigators (sponsors who personally perform all or part of the clinical testing). Sixty-seven, or 39 percent, of the 172 clinical investigators had not complied with agency requirements for informed consent. Twenty-six, or 50 percent, of the 52 sponsor/investigators had not complied.

Violations included failing to obtain consent and using forms containing various deficiencies, including exculpatory language through which the patient is made to waive or appear to waive his or her legal rights or to release the physician or the institution from liability for negligence should adverse effects occur. (See ch. 3.)

INDEPENDENT THIRD-PARTY REVIEW

Some clinical investigators use institutionalized subjects, such as those confined to a hospital, nursing home, prison, or home for the mentally retarded. Because such subjects may be more vulnerable to abuse or exploitation by research projects than the general population, the Food and Drug Administration since April 1971 has required that an institutional review committee be established for initial approval and continuing review of such studies. (See p. 42.)

Although Food and Drug Administration regulations state that, in addition to the sponsor's continuing responsibility to monitor the study, the agency will inspect institutional review committees periodically, the agency does not know the number and locations of all committees and has inspected relatively few. As of October 1974 the Bureau of Drugs had inspected 25 committees since 1971, when they were first required to be established. The Bureau of Biologics had never inspected a committee and was not

aware of the regulations concerning such inspections. (See pp. 43 and 44.)

The inspections showed that frequently the committees had not adequately reviewed new drug studies. The Food and Drug Administration had scheduled inspections at two institutions but found that the institutional review committees had not been established. (See pp. 44 to 48.)

THE AGENCY'S AUTHORITY OVER CLINICAL INVESTIGATIONS SPONSORED BY FEDERAL AGENCIES

At the time of our review, the Department of Defense was sponsoring 53 clinical investigations and the National Institutes of Health was sponsoring 222.

A question exists as to whether the Food and Drug Administration's regulatory authority under the act extends to clinical investigations sponsored by Federal agencies. (See p. 52.)

The agency had not inspected clinical investigations sponsored by the Department of Defense and the National Institutes of Health until GAO requested that some be inspected. The inspections concerning the Department of Defense were limited to unclassified studies. The inspections showed generally the same types of deficiencies as were found in the Food and Drug Administration inspections of non-federally-sponsored studies. (See pp. 52 to 58.)

GAO is making recommendations to the Secretary of Health, Education, and Welfare to enable the Food and Drug Administration to improve its monitoring and better control clinical investigations. (See pp. 26, 40, 50, 60, and 63.)

GAO also is recommending that the Congress clarify its intent regarding the question of the applicability of the Federal Food, Drug, and Cosmetic Act to Federal agencies. (See p. 60.)

The Department of Health, Education, and Welfare (HEW) did not dispute GAO's findings but questioned whether some of the recommendations provided the most appropriate solution to the problem. However, HEW generally agreed that regulation of clinical investigations needed strengthening. (See pp. 27, 40, 50, 60, 64, and app. VI.)

HEW pointed out that the Food and Drug Administration must carry out many complex, and sometimes competing responsibilities in evaluating the safety and effectiveness of new drugs. Recognizing the limited resources available for these activities, HEW said emphasizing one aspect will diminish the effort that can be directed at other aspects of the regulation of investigational new drugs. (See p. 27.)

To help the agency strengthen its monitoring activities, on April 22, 1976, the President asked the Congress for an additional $16.3 million in a fiscal year 1977 budget amendment to increase efforts in certain agency program areas, including the monitoring of preclinical and clinical testing of new drug products. (See p. 51.)

The Deparment of Defense concurred in GAO's conclusions and recommendations pertaining to it. (See p. 60 and app. V.)

CHAPTER 1

INTRODUCTION

In late 1961, Thalidomide, a sedative not approved for marketing in the United States, was being tested in pregnant women suffering from insomnia and morning sickness. Although approved in Europe as safe for general use, the drug proved to be teratogenic, causing a number of crippling birth defects, such as the lack of arms and legs. The major impact of the tragedy was avoided in the United States. However, premature distribution of Thalidomide and other inadequately tested drugs and a recognition of the ethical need to minimize risk to human test subjects were two factors that led to passage of the 1962 Kefauver-Harris Amendments to the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301).

REQUIREMENTS OF LAWS AND IMPLEMENTING REGULATIONS

Under the 1962 Kefauver-Harris Amendments and implementing regulations for investigational use of new drugs, the Food and Drug Administration (FDA), Department of Health, Education, and Welfare (HEW), is required to closely control the clinical (human) testing of new drugs. The FD&C Act requires that, before a new drug may be introduced into interstate commerce, FDA must approve it for safety and efficacy. Before 1962 there was no requirement that FDA be notified that drugs were being tested on humans or that a new drug be proven effective for its intended use. While chemical drugs are regulated under the FD&C Act, biological drugs are subject to both the FD&C Act and section 351 of the Public Health Service Act, as amended (42 U.S.C. 262). The latter requires that biological drugs shipped interstate be licensed to insure they are safe, pure, and potent as well as safe and effective under the FD&C Act. FDA administers the FD&C Act and the drug provisions of the Public Health Service Act.

The FD&C Act defines a "new drug" as any drug not generally recognized, among qualified experts, as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling. A new drug may be an entirely new substance or a marketed drug being tested for a new indication (that is, a condition for which the drug is not approved).

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 circumstances. This

may involve shipping an unapproved drug interstate to qualified experts (clinical investigators) for testing.

According to FDA's 1963 drug regulations, a sponsor is the person who assumes responsibility for investigating a new drug, including the primary responsibility for monitoring the clinical investigators' activities. Sponsors are generally drug manufacturers, private and government institutions or agencies, or physicians.

In a later consideration of the sponsor's responsibility, FDA in 1972 sought the advice of the National Academy of Science/National Research Council. Their views generally conformed with the FDA requirements, so FDA did not revise its regulations.

FDA defines a "clinical investigator" as any person licensed in the healing arts, such as a physician or dentist, qualified to make studies with investigational drugs. Clinical investigators must receive FDA approval for participation in the study. A sponsor who personally performs all or part of the clinical testing is referred to as a sponsor/investigator.

Investigational new drug applications

Since June 1963 FDA has required the sponsor to submit an investigational new drug (IND) application to exempt the new drug from the ban on interstate shipment of unapproved drugs, thus permitting it to be shipped for clinical studies. The evidence of safety and efficacy obtained from such studies is included in either a new drug application submitted by persons seeking to market a new drug product or a license application submitted by persons seeking to market a biological product.

Under FDA procedures issued August 14, 1970, the sponsor, after submitting an IND application, must wait 30 days before beginning clinical tests. This delay enables FDA to review the application to make certain it contains necessary information and to insure that patients will not be exposed to unwarranted risks. Before August 14, 1970, the sponsor was free to begin testing immediately after submitting the IND application to FDA.

FDA's regulations (21 C.F.R. 312) governing new drugs state that the IND application must include:

1. A statement covering all information available to the sponsor derived from preclinical investigations,

including studies made on laboratory animals, and from any clinical studies and experience with the drug, from which the sponsor has concluded that clinical tests can be conducted with reasonable safety.

2. The name of each investigator and a summary of his or her experience and training which the sponsor considers appropriate to qualify the investigator as a suitable expert to investigate the drug.

3. An overall outline of any phase or phases of the planned investigations, including detailed plans of study (called protocols) for use in the proposed testing during the clinical investigation.

In addition, the regulations require the sponsor--as a condition for IND application approval--to 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, or 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 when the drug's risks are expected to outweigh its potential benefits.

Within FDA the Bureau of Biologics regulates the testing of biological products and the Bureau of Drugs regulates the testing of all other human drugs. Before July 1, 1972, the Bureau of Biologics was under another HEW constituent agency, the National Institutes of Health (NIH), and was known as the Division of Biologics Standards.

When received by FDA, an IND application is analyzed by a review team consisting of a medical doctor, a chemist, and a pharmacologist, who seek to determine whether there is adequate data from short-term animal studies and in vitro

tests, 1/ as well as adequate manufacturing controls, to conclude that it is reasonably safe to study the drug in humans. FDA must complete this review and notify the sponsor of any safety problems within 30 days after receiving the IND; if FDA raises no objections during this time, the sponsor may start human trials. Then the review team must periodically review the IND file, including all new data submitted.

Clinical investigations are divided into three phases.

--Phase I begins when the new drug is first introduced into healthy 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 I varies, generally ranging from 20 to 50.

--Phase II covers the initial trials on a limited number of patients, generally no more than 100 to 200, to test pharmacological actions in preventing or controlling a specific disease.

--Phase III 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. Phase III trials may include several thousand persons.

Long-term animal tests, generally lasting from 1 to several years, are conducted concurrently with clinical tests and are designed to show the drug's long-term effects.

The data on a new drug collected during the three phases of testing in humans and long-term animal testing is the primary basis on which FDA approves a sponsor's new drug application or license to market the drug. Therefore, such data must be accurate and reliable.

Before permitting a clinical investigator to participate in a new drug study, FDA requires the sponsor to obtain a certification that the investigator understands and will adhere to the requirements of the law and regulations governing clinical investigations, including the requirement to

---

1/Conducted in test tubes or in glass, as opposed to tests in man or animals.

obtain informed consent of test subjects or their representatives before administering the drug.

In some cases tests involve institutionalized subjects--such as those confined to a hospital, nursing home, or prison. Therefore, since April 1971 FDA has required that, in addition to its own reviews, an initial approval and continuing review of the study be made by an institutional review committee (IRC).

From June 1963, when sponsors were first required to submit IND applications, through fiscal year 1974, FDA granted about 11,000 IND exemptions. The approximate number of active sponsors, IND exemptions, clinical investigators, and test subjects under regulation by the Bureau of Biologics and the Bureau of Drugs at June 30, 1974, follows.

	Number under regulation by Bureau of Drugs	Number under regulation by Bureau of Biologics
Sponsors	1,200	200
INDs	4,200	415
Clinical investigators	5,000	4,400
Test subjects	160,000	88,000

The percentage of INDs under regulation by each bureau and type of sponsor is shown below.

Type of sponsor	INDs under regulation by Bureau of Drugs	INDs under regulation by Bureau of Biologics
	(percent)	
Drug company	36	50
Sponsor/investigator	44	17
Federal institution	7	21
Non-Federal institution	13	12
Total	100	100

At July 18, 1974, FDA's inspection force included 148 inspectors specially trained in drugs and drug testing who conducted inspections to determine if sponsors, clinical investigators, and IRCs were complying with the law and regulations. During fiscal year 1974 the specially trained inspectors spent an average of about 20 percent of their inspection time on clinical investigations of new drugs,

including methadone; 44 percent on other drug-related work; and 36 percent on products other than drugs.

FDA has administrative and legal enforcement actions available if it finds the law and regulations are not being followed. (See p. 21.)

NATIONAL RESEARCH ACT

Public and congressional concern over protection of human subjects in biomedical and behavioral research led to passage of the National Research Act (Public Law 93-348) on July 12, 1974. The act establishes the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, composed of 11 members appointed by the Secretary of HEW.

The act requires that the Commission be composed of individuals distinguished in medicine; law; ethics; theology; the biological, physical, behavioral, and social sciences; philosophy; humanities; health administration; government; and public affairs, including five individuals who are or have been engaged in biomedical or behavioral research involving human subjects.

The Commission's duties are to identify the basic ethical principles and develop guidelines for conducting biomedical and behavioral research involving human subjects. In addition, the Commission was required to investigate specific issues, such as (1) the use of children, prisoners, and mental patients in research projects, (2) the assessment of risk-benefit criteria in biomedical research, (3) the nature and definition of informed consent, (4) the nature and extent of fetal research, and (5) the use of psychosurgery in the United States. Commission members were appointed in October 1974, and the Commission's work is in progress. The Commission's final report on its investigations is due to be provided to the Secretary of HEW in December 1976.

The act provides that after 2 years the Commission will be replaced by a permanent National Advisory Council for the Protection of Subjects of Biomedical and Behavioral Research. The Council will provide the Secretary with recommendations concerning the protection of human subjects and review the changing status and trends of biomedical research. However, Senate bill 2515, introduced on October 9, 1975, would reestablish the Commission as a Presidential Commission, broadening its jurisdiction and its membership.

Also, the National Academy of Sciences, on February 18 and 19, 1975, convened a public forum on "Experiments and Research

with Humans: Values in Conflict." The forum discussed the ethical and legal issues involved in biomedical experiments on human beings, placing special emphasis on children, the poor, prisoners, and military personnel, as well as fetal research. The four areas examined were (1) perspectives of biomedical research, (2) individual risks versus societal benefits, (3) regulatory, judicial, and legislative processes, and (4) future policy options. Although the Academy forum provided for public discussion and debate on the issues, it did not recommend improvements in human research activities.

CHAPTER 2

NEED FOR AGGRESSIVE MONITORING AND ENFORCEMENT IN CLINICAL INVESTIGATIONS

FDA has not effectively regulated clinical investigations of new drugs. At any time about 4,000 drug investigations are in progress, involving about 10,000 investigators and tens of thousands of human subjects. Between 600 and 1,100 new IND applications are filed each year. Poorly conducted clinical investigations unnecessarily expose human subjects to potential hazards. FDA's system of new drug regulation depends heavily on the accuracy of the data submitted by the sponsors. FDA acknowledges that, to protect patients and insure the quality of submitted data, FDA must monitor the performance of clinical investigations. Such monitoring is necessary for FDA to evaluate whether sponsors are effectively carrying out their responsibility for monitoring their clinical investigators.

FDA's monitoring has been limited, however, and FDA has not aggressively enforced compliance with its investigational new drug regulations. As a result, it is not effectively fulfilling its responsibility to (1) regulate clinical investigations, (2) protect the human test subjects from unnecessary dangers associated with experimental use of new drugs, and (3) protect the public from dangers from new drugs approved for marketing by insuring that the approval decision was based on accurate test data.

LIMITED MONITORING DIMINISHES REGULATORY EFFECTIVENESS

Although the 1962 Kefauver-Harris Amendments required FDA to closely control clinical investigations, FDA's monitoring has been limited. Until June 1974 FDA did not have a comprehensive plan for monitoring clinical investigations and evaluating compliance with its regulations.

In 1972 FDA began a special survey in which it inspected 15 sponsors and 155 of their clinical investigators, and in 1974 it inspected, at our request, 83 more clinical investigators. Before 1972 FDA monitoring was limited to about 40 inspections of clinical investigators suspected of wrongdoing. In most inspections since 1972, FDA found that clinical investigators were not fully complying with the law and FDA regulations and that sponsors were not adequately monitoring their clinical investigators.

Special survey

FDA began the special survey in July 1972 to assess the practices and procedures of sponsors and their clinical investigators. The last inspection was completed in June 1974. Our review of the inspection results indicated that, of the 155 clinical investigators inspected, 115 (74 percent) failed to comply with 1 or more requirements of the law and regulations. The percentage of clinical investigators who failed to comply with each of six requirements checked by FDA follow.

Requirements	Percent failing to comply
Informed patient consent	35
Drug accountability	50
Protocol adherence	28
Records accuracy	23
Records availability	22
Investigator's role in study	12

Except for informed consent (see ch. 3), the requirements and related deficiencies are described below.

Drug accountability--The investigator must accurately record the amount of drug received from the sponsor and distributed to test subjects. Only authorized individuals should distribute investigational drugs. At the conclusion of the study, the investigator must return any unused drug to the sponsor. Also, should a drug be found to cause health hazards serious enough to require recalling the drug supplies, lack of proper drug accountability could impede or preclude the recall, leaving the hazardous drug in the hands of the unsuspecting patients. Thus, drug accountability is important from the standpoints of patient protection (receiving the proper dosage under the supervision of a qualified investigator) and preventing unauthorized use of the drug.

Protocol adherence--The investigator must adhere to the protocol, a detailed plan for conducting the investigation, agreed upon by both sponsor and investigator and submitted to FDA. Significant changes in direction or scope of the investigation must be reported to the sponsor and by the sponsor to FDA. Deviations from the agreed-upon protocol may invalidate study data. In such cases, human test subjects are unnecessarily placed at risk because the study results cannot be used.

Records accuracy--The records must accurately reflect the patient's condition before, during, and after the study and the type of laboratory work done and other therapy administered during the study. Accurate records show that the clinical investigator has provided proper care and attention to the study. Perhaps more important, the validity of conclusions derived from the study and ultimate market approval depend upon the accuracy of the study records.

Records availability--The investigator must keep accurate case records for at least 2 years after the drug's approval for marketing or withdrawal from clinical trial. Maintaining records is particularly important for followup should unexpected results develop during or after a study.

Study role--The drug may be administered only by the investigator or a qualified individual under his or her direct supervision. To insure that only qualified investigators use the drug, the investigator may not provide the drug to individuals not mentioned in the agreement with the sponsor. To insure proper supervision of the drug's use, the investigator may not delegate responsibility for the investigation to subordinates or include as study subjects individuals whose geographical location does not permit close observation and followup.

Details on FDA's inspection findings concerning several sponsors and their clinical investigators follow. In addition to the deficiencies discussed in each case, deficiencies were found in consent procedures. (See ch. 3.)

Sponsor A

In 1973, as part of its special survey, FDA inspected sponsor A and nine of its clinical investigators conducting phase II and phase III trials of a vaginal cream for the treatment of moniliasis--an infection caused by yeast-like fungi. In seven of the nine clinical investigations for which we obtained a copy of FDA's inspection report, over 290 women participated.

All nine clinical investigators were deficient in compliance in one or more of the six FDA requirements. FDA's letter to the sponsor summarized the deficiencies as follows.

	Number of investigators
Failed to maintain proper drug accountability records	7
Deviated from protocol	5
Maintained inaccurate case records	4
Failed to maintain patient records to support case reports	3

FDA told sponsor A that few investigators were aware of the requirements to maintain proper drug accountability--an indication of the sponsor's lack of proper monitoring. Although FDA regulations require that unused drugs be returned to the sponsor, some investigators kept the unused drug supplies after completing their study. One investigator said that after study completion he sometimes retains the unused portion to use on other patients if he "thinks it is a drug of choice." FDA inspectors' attempts to reconstruct drug accountability records for several studies revealed various amounts of unaccountable overages or shortages.

The inspections also revealed numerous deviations of varying degrees from the protocol. For example, one investigator omitted required laboratory studies (hematology, urinalysis, and biochemical properties) on 40 percent of his patients. He said he obtained oral approval from the sponsor's monitor to omit the studies. FDA advised the sponsor that, if deviations are authorized, such authorizations must be in writing and that careful monitoring can prevent most deviations.

Another investigator who deviated from the protocol a number of times said he did so on his own initiative, without the required knowledge and concurrence of sponsor A. In one case this investigator included in the clinical study a patient who did not meet the protocol selection criteria. The investigator said he had "slipped up" and should not have admitted her to the study.

One other investigator failed to follow the protocol requirements for

--post-therapy examinations,

--Pap smear tests,

--the alternating of two drugs administered to patients, and

--treatment of moniliasis when it recurred.

Record inaccuracies noted in four studies included numerous discrepancies between patient records and case reports submitted to FDA. In one study, the case report showed that two apparently different patients--one age 22, admitted to the study in January 1973, and the other age 32, admitted in November 1972--had the same name. The investigator's assistant stated "there had been a mix-up somewhere." In another study, tests reported in the case reports could not be substantiated by raw data. The investigator told the FDA inspector that if the test results were not in the patients' records, the tests probably were not made. FDA advised sponsor A that when patient records are not available, the credibility of a study can be questioned.

Sponsor B

This was a phase III study of an antibiotic used to treat a variety of bacterial infections. One investigator's study lasted 18 months and involved 155 human test subjects. Most of the study was done by 18 resident physicians at 3 hospitals. FDA concluded that the investigator's management of the study was unsatisfactory, authority was delegated and diffused to the vanishing point, and the result was a weakened study. Drug accountability was inadequate, and laboratory and treatment records in many cases were inaccurate. For example:

--The investigator failed to keep a complete record of all drugs received, dispensed, or returned to the sponsor. He said he thought some had been returned but could not find documentation of that fact. He said the residents may have given supplies of the drug to other residents not in the study.

--Laboratory and treatment records contained errors in (1) transcribing laboratory reports, (2) reporting dates of treatment, and (3) calculating total days of treatment. The investigator said this was a constant problem with the resident physicians and that he also had problems with residents failing to complete case reports when patients die after receiving only one or a few doses of an investigational drug. Review of the laboratory results in the files of 8 patients disclosed 54 discrepancies from the results reported to sponsor B.

--Deviations from the protocol included failing to perform required laboratory tests; giving patients concomitant antimicrobial therapy for treatment of the condition for which the experimental drug was being used; and admitting patients that did not meet the selection criteria, including some with pseudomonas (a type of bacteria).

The protocol states the experimental drug should not be used to treat pseudomonas. The FDA inspector's review of 10 patients' records revealed 2 were admitted with pseudomonas and 1 was treated for the condition with the experimental drug. Review of the autopsy reports for the six test subjects that died indicated the presence of pseudomonas in one patient but did not implicate the drug in the death. In another deviation from protocol, records for a 12-year-old patient indicated the possibility that a 10-day supply of the injectable antibiotic was given to the patient's mother for administration at home. When asked if he considered this an approved practice for investigational studies, the clinical investigator said the parent of one subject had been a nurse and this might have been the one.

The investigator told the FDA inspector he considered this study to be insignificant research since he knew through experience that the drug would work and would not hurt anyone. He also stated he did not consider all the case reports submitted to sponsor B to be acceptable for evaluation but did not tell the sponsor so. He said the evaluation was between the sponsor and FDA. At the conclusion of the inspection, the investigator invited the FDA inspector back to review one of his better investigations.

Sponsor C

This was a phase III study of a drug used to treat rheumatoid arthritis. An excerpt from FDA's letter to the clinical investigator concerning the inspection findings follows.

> "We have reviewed [the FDA inspector's] report and find multiple deficiencies in your investigational procedures."
>
> * * * * *
>
> "2. Drug accountability was haphazard, with 992 tablets unaccounted for at the time of [the inspector's] visit.
>
> "3. Failure to follow protocol.
>
> "a. No prestudy x-rays within 3 months on 8 patients.
>
> "b. Concomitant therapy-6 patients.
>
> "c. Diagnosis not indicated-5 patients.

"d. Documentation of the existence of the treated disorder * * * present in only one patient.

"We consider the above deficiencies to be significant deviations from the Investigational Drug Regulations and feel that they represent dereliction of your responsibilities as a clinical investigator."

Sponsor D

This was a phase III study of a drug intended to reduce the appetite of obese patients. Sixty test subjects participated in the study. FDA's letter to the clinical investigator stated:

"We must conclude that you did not give proper consideration to your obligations as an investigator of new drugs. Our conclusion is based on the following:

"1. You did not have any contact with any of the patients participating in your study."

* * * * *

"3. The review of records generated in the study disclosed multiple discrepancies relating to patient numbers, which, in turn, created a most confusing picture of the actual medication schedule.

"4. Two patients received concomitant medication with other [appetite-suppressing] agents. This reflects a lack of proper control of this study.

"We would remind you that repeated or deliberate failure to comply with the Regulations * * * could lead to loss of [the investigator's] entitlement to receive investigational new drugs."

Although not mentioned in the letter, drug accountability was nonexistent. The clinical investigator said he had no record showing the amount of drug received, date received, amount used, and amount destroyed when the study was completed.

The inspection also disclosed that some adverse reactions to the drug reported to sponsor D were not recorded in the hospital outpatient records. In another case a possible reaction noted in the outpatient record was not reported to the sponsor. A small nodule was noted in the patient's breast while on the study and was removed by surgery after the study ended. The assistant to the clinical investigator said that the nodule was not malignant and that she did not believe discovery of a nodule in a breast was unusual or alarming in a study of an investigational drug.

The clinical investigator told the FDA inspector he had been making clinical investigations for 16 years and had never before been inspected.

FDA's evaluation of special survey findings

The Commissioner of FDA, in congressional hearings on July 10, 1975, pointed out that a 1970 pilot survey of sponsors revealed that they were reluctant to discuss the IND regulations with their clinical investigators lest they antagonize them. Furthermore, it was found that sponsors did not routinely examine the investigator's raw patient data. He stated that the 1972 special survey results reflect the same situation. The sponsors, in seeking out capable physicians to conduct their studies, "appear loath" to discuss IND fundamentals with an expert clinician.

The Commissioner said that the inspectional findings at the investigator level reflect the consequences of this reluctance and that improvements were needed to raise the levels of compliance. He concluded that the sponsors are in the best position to raise these levels by more thorough supervisory contact with their investigators. He pointed out that sponsors, in their discussions with investigators, should stress and detail not only the protocol to be used but also the Investigation Drug Regulations to be followed.

FDA inspections made at GAO's request

We found that FDA had never inspected clinical investigators working for Federal sponsors or as a sponsor/clinical investigator. It also had not inspected sponsors or clinical investigators regulated by the Bureau of Biologics.

The Director, IND Staff, Bureau of Biologics, said he lacked the resources to make inspections. He was not aware that about 148 FDA field inspectors, specially trained to inspect clinical investigations, were available for such inspections. (This and other matters concerning lack of

coordination between the Bureau of Drugs and the Bureau of Biologics are discussed in ch. 6.)

Because of FDA's complete lack of data on these important and sizeable segments of clinical investigation activities, we requested FDA to inspect a sample of clinical investigators from each segment. The results of the inspections of federally sponsored clinical investigations are discussed in chapter 5. Results of the other inspections made at our request are discussed below.

Bureau of Drugs

In about 44 percent of the new drug clinical investigations, physicians act as both the sponsor and investigator. In these cases, the study is usually done for basic research, rather than to accumulate data needed to prove the drug is safe and effective for marketing. Unlike studies sponsored by a drug company, studies made by a sponsor/investigator are not subject to independent monitoring by sponsors. In such cases, FDA monitoring becomes even more important. We found, however, that the Bureau of Drugs had never inspected studies conducted by sponsor/investigators.

At our request, FDA inspected a sample of 35 sponsor/investigators from the 225 that submitted IND applications to the Bureau of Drugs during fiscal year 1973. Compliance levels were low--generally no better than compliance levels disclosed by FDA's 1972 special survey. Compliance in drug accountability was much lower. The Bureau of Drugs' Scientific Investigations Staff expressed surprise at the disclosure. All 35 sponsor/investigators failed to comply with one or more requirements of FDA's regulations.

Although the ability to project the findings to all sponsor/investigators was limited by the small number inspected, Bureau of Drugs officials said general trends were fairly clear. The percentage of sponsor/investigators that failed to comply with requirements that Bureau officials considered most important are shown below.

Requirements	Percentage failing to comply
Informed patient consent	a/44
Institutional review committee	34
Communication with FDA and collaborators	85
Drug accountability	67

a/As discussed on pages 32 and 33, we evaluated the consent forms using FDA's criteria and found the failure rate to be 85 percent.

(Ch. 4 discusses deficiencies found in the performance of IRCs.)

The third category--communication with FDA and collaborators--represents a combination of failure rates in several areas. For example, 76 percent failed to notify FDA of changes in protocol as required, 48 percent failed to submit timely annual progress reports, 15 percent failed to wait the required 30 days before administering the drug, and all the sponsor/investigators whose patients experienced alarming adverse reactions to the drug failed to report them.

The results of FDA's inspection of two sponsor/investigators follow.

Sponsor/investigator A--The drug in this study was being used to treat three hospitalized patients having generalized lipodystrophy (a disturbance of fat metabolism causing grotesque disfigurement).

--Two patients suffered alarming adverse reactions about 6 weeks and 1 week, respectively, before the FDA inspection. These reactions, which were not reported to FDA until the day after the inspection, included severe depression, tiredness, unsteadiness of gait, anxiety, and insomnia. The investigator said the reactions were alarming because, in the patients' conditions, they might cause suicidal tendencies.

--Drug accountability was not properly maintained, and 100 capsules were shipped to another investigator without FDA's knowledge and approval and without the required signed statement from the investigator receiving the capsules that he understood his responsibilities under FDA regulations.

--No control patients were selected for the study as required by the protocol.

--Approval by an IRC was not obtained until 1974, although the study began in 1972. The investigator said he was not aware of the requirement.

Sponsor/investigator B--This was a study of a drug used to treat mycosis fungoids, a rare chronic skin disease. The drug was known to produce cancer in tests on laboratory animals. FDA's letter to the investigator stated:

"Several aspects of our investigator's report are of concern to us. We note that you did not always get written consent from your office

practice patients. We further note that you provided the drug to three other physicians not directly responsible to you, and whose names and Investigator Statements * * * were not supplied to us. In addition, we note that one patient was treated prior to your filing for an IND. Finally, the report indicates that no drug accountability procedures were in effect."

Bureau of Biologics

At our request, FDA inspected a sample of 23 sponsor/investigators and 25 clinical investigators working for commercial sponsors. FDA selected the clinical investigators from the INDs submitted during fiscal years 1972 and 1973. FDA found that the level of compliance observed during the 48 inspections ranged from "substantial deficiencies" to "substantial or complete compliance" with provisions of the law and regulations, as shown below.

Level of compliance	Sponsor/ investigators	Investigators for commercial sponsors	Total
In substantial compliance	14	14	28
Poor recordkeeping only	2	10	12
Noncompliance in substantial areas	7	1	8
	23	25	48

Although FDA judged 28 to be in substantial compliance in all areas, in at least two areas--patient consent and drug accountability--the large majority of the 48 inspected failed to comply. Thirteen of the 23 sponsor/investigators and 19 of the 25 commercial investigators failed to obtain or properly obtain patient consent. FDA found most consent forms to be poor or incomplete. Failure to maintain proper drug accountability was a problem for 16 sponsor/investigators and 14 commercial investigators.

Poor recordkeeping included problems in data compilation, drug accountability, and the listing of assistant investigators. Noncompliance in substantial areas included refusing to provide progress report information to the sponsor, failing to inform FDA that additional principal clinical investigators had been added to the study, failing to obtain written patient consent, and failing to obtain IRC approval.

FDA concluded that the inspection results demonstrated the importance of the Bureau of Biologics' developing an inspection monitoring program to promote full compliance

with the regulations. FDA is considering sending a letter to each sponsor of biological products summarizing the inspection findings. In its letter, FDA plans to express its concern that clinical investigators have not been complying with the law and FDA regulations.

Two investigators found in noncompliance in substantial areas were also, according to FDA, deficient in medical performance. Both were sponsor/investigators and are discussed below.

Sponsor/investigator C--This was an ongoing phase II study of a new drug used to reduce the rejection rate among kidney transplant patients. About 650 patients were treated; 85 died. The sponsor/investigator did not attribute any of the deaths to the drug. The deficiencies FDA found included:

--Failure to obtain written patient consent.

--Failure to report to FDA four cases of an alarming adverse reaction (renal artery thrombosis, a blood clot in an artery of the kidney).

--Failure to report patient deaths to FDA.

--Failure to submit annual progress reports.

--Failure to obtain FDA approval of protocol modifications.

--Failure to wait the required 30 days before administering the drug.

--Failure to obtain FDA approval to use 15 additional clinical investigators in various States.

The Director, IND Staff, Bureau of Biologics, said that correspondence with the clinical investigator after the inspection indicated that even oral patient consent for use of the investigational drug had not been obtained. The Director said FDA regulations require that deaths be reported immediately only when--in the opinion of the sponsor and clinical investigator--the death is alarming and is attributed to the drug. (The regulations require that any alarming adverse effect which may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported immediately.) The Director added that, if the investigator does not believe death was caused by the drug, he or she can wait and note the death in the annual progress report without reporting the surrounding circumstances. In this case, however, the progress report was not submitted until the study was over 2 years old.

The Director said the unapproved deviations from protocol were significant and could adversely affect patient safety.

Sponsor/investigator D--This study used an experimental radiobiological in 37 hospitalized patients. According to the clinical investigator, the patients were, for the most part, mentally incompetent and averaged 69 years of age. The inspection revealed that the investigator failed to follow the protocol requirement for administering iodides to the patients, before injecting the radioactive drug, to prevent uptake of the drug by the thyroid gland.

The investigator said the iodides were not administered because the patients were old, administration of the iodides causes general discomfort, and the patients were "all demented and difficult to orally medicate." FDA said this failure to follow the protocol constituted a clear medical hazard to the patients' thyroid glands.

Recent actions to improve monitoring

As early as 1968 FDA recognized that data submitted by clinical investigators was frequently unreliable and that on-site inspections of the facilities and records were necessary to insure data reliability. Not until June 1974, however, did FDA develop what it termed a "comprehensive plan for clinical investigation evaluation." According to FDA, the impetus behind developing the plan was

> "the lack of a concrete strategy * * * especially during a time of close public and congressional scrutiny resulting from the identification of unethical and non-scientific investigational studies."

The plan consists of a number of subprograms intended to enhance FDA's monitoring efforts, including:

--Standard setting to insure that regulations and guidelines are adequate.

--Education to insure that sponsors and investigators are aware of their responsibilities and of problems identified through FDA inspections.

--Coordination to insure that the Bureau of Drugs and the Bureau of Biologics use resources most efficiently in their parallel monitoring activities.

--Surveillance inspections based on representative samples of sponsors, investigators, and IRCs.

Although the plan appeared to be a step in the right direction, it had been only partially implemented. Inspections of a random sample of clinical investigators have been made under the surveillance program. However, because of higher priority projects the needed regulations and guidelines had not been published for comment as of May 1976. Problems identified in the 1972 special survey and in the inspections we requested have not been published, although the inspections were completed in 1974. The two bureaus have not achieved adequate coordination.

NEED FOR AGGRESSIVE ENFORCEMENT OF THE LAW AND REGULATIONS

FDA has not aggressively regulated clinical investigations. Although inspections have revealed a wide range of deficiencies, FDA has not taken effective enforcement action to achieve correction.

The FD&C Act and FDA regulations provide for administrative and legal actions against those who violate requirements. FDA has made only limited use of these enforcement actions. Administrative actions include:

--Sending an information letter advising a firm or person of violations of law and regulations.

--Disqualifying clinical investigators from eligibility to receive investigational drugs if they repeatedly or deliberately violate the law or regulations.

--Terminating a sponsor's IND exemption for various reasons. (See pp. 24 and 25.)

The following legal actions may be initiated through the Department of Justice:

--Prosecuting an individual under title 18 of the U.S. Code for submitting fraudulent data to the Government.

--Enjoining an individual or firm from violating the FD&C Act and FDA regulations.

--Seizing any drug product that is adulterated or misbranded, or is a new drug without an IND, when introduced into, or while in, interstate commerce.

Information letters

In 1973 the Bureau's Director, Scientific Investigations Staff, wanted to send letters pointing out deficiencies to

sponsors and clinical investigators who had been inspected under the 1972 special survey. The Director of the Bureau of Drugs, however, believed that sending the letters would be unfair because the inspections were part of a survey to gather information, not to determine noncompliance with the regulations. He also doubted the legality of the letters and refused to sign them until a legal determination was made.

The HEW Assistant General Counsel, Food, Drugs, and Environmental Health Division, in his response to the Director's request for a legal determination, stated:

> "Contrary to your note of 10/23/73 attached to the file, I do not believe that the letter * * * is either harsh or an over-kill. Nor do I agree that it should be 'tempered' with equivocal statements. The investigators who receive letters like this are grown men. They must understand the importance of the work they are doing, and the fact that the law imposes obligations upon them * * * I see no more reason to coddle the medical profession than I do to coddle drug manufacturers or food warehouse owners. Where criticism is deserved, it should be set forth in a candid and honest manner."
>
> * * * * *
>
> "The entire approach is sound from both a legal and a public policy standpoint."

Subsequently, the Bureau of Drugs sent information letters to each of the 15 sponsors inspected as part of the 1972 special survey describing the deficiencies of the sponsor's investigators. Although the letters emphasized that the deficiencies could have been minimized if not completely eliminated by careful and conscientious monitoring by the sponsors, the Bureau did not require the sponsors to respond and inform FDA of corrective actions taken to improve their monitoring. Instead, the letters closed with: "We request that you furnish us with any comments or proposals you may wish to offer on these subjects." Only 7 of the 15 sponsors responded. Three outlined procedures they had instituted as a result of FDA's inspections; three simply said that FDA's survey would help them improve their monitoring procedures; and one met with the Bureau of Drugs to outline its monitoring procedures.

FDA also sent letters to each of the 155 clinical investigators. About 40 whose work was found generally or completely satisfactory were sent courtesy letters; 19 whose

work was found unsatisfactory or violative of regulations were sent letters containing specific admonitions or warnings; and the remainder were sent a letter delineating specific areas needing improvement. Response to the letters from the investigators was sparse; most respondents rebutted, acknowledged, or questioned (or all three) the survey findings. Several indicated appreciation of the visit and promised to correct deficiencies.

Disqualification of the clinical investigator

The only administrative action specified in the FDA regulations directly applicable to clinical investigators is disqualification. If the Commissioner of FDA finds an investigator has "repeatedly" or "deliberately" violated the regulations, he may declare the investigator ineligible to receive investigational drugs--that is, he is disqualified from further participation in investigational drug studies.

The Bureau of Drugs has disqualified 20 clinical investigators since the Kefauver-Harris Amendments of 1962. Five were later reinstated when, in accordance with the regulations, they assured FDA that the problems would not reoccur. The Bureau of Biologics has disqualified 10 clinical investigators, 5 of whom were later reinstated.

The Bureau of Drugs disqualified the 20 investigators because they submitted false information, seriously deviated from the protocols, and/or violated other FDA regulations. The Bureau of Biologics disqualified the 10 investigators because they failed to submit progress reports. No investigator has been disqualified for any of the many violations of the regulations disclosed by the inspections under the special survey or the inspections we requested.

The Bureau of Biologics has made no disqualifications since 1971 and the Bureau of Drugs made none from 1970 through 1974. Although disqualifications had been recommended to the Director of the Bureau of Drugs during that period, he said he was not given evidence of repeated violations. The Bureau of Drugs has seldom inspected a clinical investigator more than once. The Director, Scientific Investigations Staff, who is responsible for the Bureau's monitoring efforts, said FDA has no policy or procedures for making routine followup inspections when violations are found. She said she had no reason to doubt that the investigators would take corrective actions.

She added that the recent trend away from disqualifying clinical investigators reflects FDA's growing emphasis on education rather than enforcement. FDA hopes this emphasis

will stimulate sponsors and clinical investigators to voluntarily improve the conduct of clinical studies. Besides publishing the problems found during FDA's inspection, the education effort includes giving each investigator inspected in the future a copy of FDA requirements concerning clinical investigations.

Educating sponsors and clinical investigators about their responsibilities is certainly needed and should result in improved drug studies and better protection of test subjects. We do not believe, however, that investigators who fail to comply with the regulations can be excused on the basis of ignorance. Before being approved by FDA to conduct a clinical investigation, each investigator must submit a signed FDA Form 1572 or 1573 which specifies his responsibilities and certifies that he is aware of and accepts them. Moreover, the requirements are also published in the Code of Federal Regulations, and sponsors are responsible for selecting only qualified clinical investigators, experts in their field.

FDA officials told us that numerous problems hamper effective use of the disqualification sanction. Evidence of "repeated" or "deliberate" violations is difficult to obtain.

FDA officials have variously interpreted the term "repeatedly." According to FDA's Associate Chief Counsel for Drugs, the term means that the violation was found several times during a single inspection by FDA. The Director of the Bureau of Drugs said it meant that violations were found more than once in the lifetime of the clinical investigator. The Director, Scientific Investigations Staff, said the meaning of the term is frequently debated because the regulation is hard to interpret.

The Director of the Bureau of Drugs acknowledged that the policies and procedures for handling poor clinical investigators need clarification and revision. He said present procedures are cumbersome and offer limited options--basically disqualification.

Termination of the IND exemption

An effective but seldom used tool is the authority to terminate the IND exemption. Because termination directly affects the sponsor, the sponsor is stimulated to take action concerning the clinical investigator. The Commissioner of FDA may terminate an IND exemption if he finds

--the sponsor has submitted false data or has omitted material information;

--inadequate support to conclude that clinical investigations can be initiated or continued with reasonable safety;

--evidence that the drug is unsafe or ineffective for the purposes and in the manner in which it is offered for investigational use;

--unsatisfactory manufacturing practices;

--the plan for clinical investigations of the drug is not reasonable in whole or in part, or the investigations are not conducted in accordance with the plan;

--improper labeling or commercialization of the drug;

--failure to submit progress reports at least once a year; or

--failure to report serious or potentially serious adverse reactions.

Since June 30, 1971, FDA has terminated 12 INDs in the Bureau of Drugs and 9 in the Bureau of Biologics. The reasons cited most often were insufficient information upon which to evaluate safety and failure to submit progress reports.

Legal sanctions

Since the Kefauver-Harris Amendments of 1962, four cases have been referred to the Department of Justice, which prosecuted two clinical investigators for submitting fraudulent data.

CONCLUSIONS

FDA has failed to adequately monitor clinical investigations. It has placed primary responsibility on sponsors to monitor clinical investigations; however, its inspections have shown that sponsors have not adequately assumed this responsibility. FDA has made piecemeal attempts to monitor the activities of sponsors and clinical investigators, but coverage has generally been spotty and some areas have not been covered at all. The Bureau of Drugs never inspected sponsor/investigators, and the Bureau of Biologics had not inspected sponsors or investigators until we requested that some be inspected.

As a result of inadequate monitoring of sponsors and clinical investigators, FDA lacks assurance that human test

subjects are adequately protected and that the data upon which marketing approval is based is accurate and reliable. We believe that noncompliance with pertinent laws and FDA regulations disclosed by recent FDA inspections is traceable in large measure to FDA's limited monitoring of sponsors and clinical investigators.

FDA recognized the need for better monitoring as early as 1968 but waited nearly 7 years to develop a comprehensive monitoring plan. We believe this delay in the face of the recognized need clearly demonstrates FDA's lack of aggressiveness in fulfilling its responsibilities in this important area. The plan appears to be a step in the right direction, but it has not been fully implemented; subprograms and various details have yet to be worked out.

Improved monitoring efforts, however, must be coupled with improvements in FDA's enforcement program if lasting improvements are to be achieved in the levels of compliance. FDA's monitoring efforts primarily identify specific deficiencies. But monitoring does not insure compliance. For that, FDA needs an aggressive enforcement program to deal with violators and deter others. FDA's enforcement against sponsors and clinical investigators has frequently not been sufficiently aggressive to do this.

Although we do not advocate disqualifying all clinical investigators found in violation or terminating INDs in each instance of sponsors' inadequate monitoring, greater use of all available enforcement tools is needed. The ample enforcement options available have not been fully used. Educating sponsors and investigators about their responsibilities is needed, but this should be coupled with more aggressive enforcement of compliance with laws and FDA regulations.

In addition to the problem of interpreting the terms, limiting disqualification to instances of "repeated" or "deliberate" violation of the regulations seems unnecessarily restrictive and hampers effective enforcement. The regulations should be revised to give FDA greater discretionary use of disqualification actions when regulations are violated.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to:

--Give priority to implementing the comprehensive plan for monitoring and evaluating clinical investigations regulated by the Bureau of Drugs and the Bureau of Biologics. (See p. 20.)

--Better use enforcement actions to insure corrective action by sponsors and clinical investigators when violations are found.

--Revise the regulations to give FDA greater discretionary use of disqualification actions when regulations are violated by deleting the requirement that an investigator must be found to have repeatedly or deliberately violated the regulations.

AGENCY COMMENTS AND OUR EVALUATION

In commenting on a draft of this report (see app. VI), HEW did not dispute our findings but questioned whether the proposed remedies offered constructive and effective solutions to present conditions. HEW believed that some of the specific recommendations throughout the report did not provide the most appropriate solution to the problem. However, HEW generally agreed that regulation of clinical investigations needed strengthening. HEW's comments on specific recommendations and our evaluation of them are presented in the appropriate chapters of the report.

Implementation of monitoring and evaluation plan

HEW said that the plan referred to in our recommendation was prepared in June 1974, and although its general concepts are still valid, the implementation plan for most of the specific steps is no longer accurate. HEW pointed out that FDA must carry out many complex, and sometimes competing responsibilities in evaluating the safety and effectiveness of new drugs. Recognizing the limited resources available for these activities, HEW said emphasizing one aspect will diminish the effort that can be directed at other aspects of the regulation of investigational new drugs. According to HEW, in 1975 much of FDA's monitoring resources had been redeployed to examining certain sponsor preclinical test data, the reliability of which had been questioned. HEW said that current plans for the clinical investigation evaluation program reflect these events but remain among FDA's highest priorities.

Enforcement actions

HEW said FDA believes that it is using available enforcement actions appropriately when violations are significant enough to warrant action and that changing the criteria for using enforcement actions is not likely to greatly affect the performance of clinical investigators.

HEW further stated that:

"* * * GAO * * * assumes an adversarial relationship between FDA and the research community. The goals of science and medicine and of FDA regulation are the same: ethical research, scientifically valid and useful research, research protecting and benefiting both the subjects and patients generally. Achieving these objectives requires both clear exposition of FDA policies to encourage understanding and compliance and judicious application of sanctions in those situations where clearly improper behavior is found. For the FDA to approach researchers as though their only incentive to comply is threat of FDA action, however, demeans the ethical and professional standards of these persons and is unjustified by the evidence. Moreover, a hostile FDA might produce a reluctance to cooperate with the Agency, or worse, a disincentive for research itself."

HEW pointed out that the FDA Commissioner testified on July 10, 1975, during joint hearings by the Subcommittee on Health, Senate Committee on Labor and Public Welfare, and the Subcommittee on Administrative Practice and Procedure, Senate Committee on the Judiciary, that monitoring clinical investigators is the direct responsibility of IND sponsors, who are responsible for the quality and accuracy of reports to FDA and for assuring that investigators are fulfilling their scientific and ethical commitments. HEW said that increasing FDA monitoring could signal to sponsors that FDA is replacing them in the direct supervision of investigators and thus reduce sponsor monitoring. FDA believes that improving rather than replacing the sponsors' oversight of investigators is the key to an effective, efficient solution to the problem.

Apart from specific actions against poor investigators, FDA believes that its single most helpful action will be to assure that sponsors meet their monitoring obligations. HEW said that regulations are being prepared which will define much more clearly the responsibilities of the sponsor with respect to monitoring investigations.

According to HEW these proposed regulations will require the sponsor to (1) submit to FDA written procedures for monitoring investigations, (2) assure that the investigator clearly understands his obligations before participation, (3) visit the investigator periodically to assure that protocol is being adhered to, (4) receive written approval of the institutional review committee, where applicable, before

initiating the investigational study, and (5) maintain accurate accounting procedures and records. HEW said that, collectively, these requirements will oblige the sponsor to control investigator performance in many of the same areas in which our report recommends FDA directly oversee individual investigators. HEW believes the approach of focusing on sponsors is superior because it places the legal responsibility where it properly belongs, has a much more immediate effect on all investigators, and enables FDA to verify the performance of all investigators while investing fewer resources.

We recognize that sponsors are primarily responsible for monitoring their clinical investigators. However, some FDA inspection of clinical investigators is necessary to evaluate whether sponsors are adequately carrying out this responsibility. Such FDA inspections are even more important when the clinical investigator is also the sponsor. The FDA inspections conducted at our request showed that sponsor/investigators violate requirements of the law and regulations about as much as clinical investigators.

We believe that, because FDA is responsible for regulating the research community that conducts investigations of the safety and efficacy of new drugs, it must sometimes assume an adversary role to enforce compliance with laws and regulations. Effective regulation of clinical investigations is important because FDA relies heavily on the data obtained from them in making decisions about the safety and efficacy of new drugs. Improperly conducted clinical investigations could produce false or misleading data about the drugs and expose test subjects to unnecessary risks. Aggressive enforcement of law and regulations would not demean the ethical and professional standards of the research community; rather it would serve to reenforce those standards and provide additional incentives for adherence to them.

Moreover, we believe that increased FDA monitoring of clinical investigations, accompanied by effective enforcement action when violations are noted (see pp. 21 to 25), would signal to sponsors that FDA was tightening its regulation of clinical investigators. This should in turn increase sponsor monitoring activities to insure compliance with FDA requirements.

Although FDA believes that sponsors have primary responsibility for assuring that clinical investigators comply with FDA requirements, FDA has not required sponsors to bring violative investigators into compliance. For example, FDA's special survey completed in fiscal year 1974 showed that 115 (74 percent) of the 155 clinical investigators inspected failed to fully comply with the law or regulations and that

sponsors were not adequately monitoring their investigators. In his July 1975 testimony, the Commissioner stated that FDA notified the 115 investigators of the need to improve compliance with the regulations; some received severe admonition or warning and the violations in some cases required followup inspections. According to the Commissioner, FDA advised the appropriate sponsors of the survey findings and invited their comments and proposals; most sponsors did not respond. FDA's action in these cases would not seem to impose any obligation on the sponsors to obtain investigator compliance.

FDA's proposed regulations to more clearly define the sponsor's responsibility to monitor clinical investigators should, when issued, affect the monitoring of clinical investigations. However, unless the new regulations are aggressively enforced, their effect is not likely to be much greater than that of the current regulations. Such enforcement is particularly important in view of the indications that sponsors have not adequately monitored investigators and, as the Commissioner testified in July 1975, sponsors "appear loath" to discuss IND fundamentals with expert clinicians. (See p. 15.)

A first draft of FDA's proposed regulations was completed in September 1974. As of May 1976 the regulations had not been published for public comment. Pending issuance of the new regulations, FDA should insure that sponsors carry out their responsibilities under the current regulations.

Revision of disqualification regulations

HEW stated that FDA intends to revise the regulations regarding disqualification of investigators to improve the process by eliminating unnecessary procedures, by clarifying the criteria actually used by the agency, by establishing uniform handling of actions among bureaus, and by resolving certain legal problems that have been uncovered. HEW added that clarification of the obligations of investigators, together with new regulations regarding the sponsors' responsibility to monitor studies, should substantially increase compliance observed by FDA.

CHAPTER 3

NEED TO INFORM HUMAN SUBJECTS PARTICIPATING IN NEW DRUG TESTING

FDA views informed consent as a principal means of protecting humans subjected to experimental use of new drugs. However, often the consent of test subjects is not obtained or they are not adequately informed of their participation in new drug testing because FDA regulations

--are not complied with by clinical investigators and

--are confusing and subject to misinterpretation by FDA officials as well as sponsors and clinical investigators.

The FD&C Act explicitly requires that (1) any human beings participating in an experiment with a new drug be informed of such use and (2) their consent, or that of their representative, be obtained. The two exceptions to this rule are when (1) obtaining consent is not feasible or (2) in the doctor's professional judgment, obtaining consent would be contrary to the subject's best interests.

In regulations implementing the FD&C Act, FDA has specified that a test subject (or his representative) must have the legal capacity to give consent and be able to exercise free choice. The consenting test subject must be given a fair explanation of the procedures to be followed in carrying out the drug investigation, including

--an identification of those which are experimental,

--a description of the discomforts and risks involved,

--a description of benefits that may occur, and

--a disclosure of alternative therapy available.

In addition, the form should not contain exculpatory language through which the patient is made to waive or appear to waive any legal rights or to release the physician or the institution from liability for negligence should adverse effects occur.

Written consent of persons receiving an investigational new drug in phase I or phase II tests is required by FDA regulations. However, for phase III tests the regulations read

"* * * it is the responsibility of investigators, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form. When such written consent is not obtained, the investigator must obtain oral consent and record that fact in the medical record of the person receiving the drug."

When oral consent is obtained during phase III, the clinical investigator is required to indicate in the patient's record only that oral consent was obtained. He is not required to indicate what he told the patient about the investigational drug.

FAILURE TO MEET CONSENT REQUIREMENTS

In 238 FDA inspections made since 1972, consent information was available on 172 clinical investigators and 52 sponsor/investigators. The inspections showed that many investigators failed to comply with FDA's requirements for informed consent. The number and percent of investigators that failed to comply follows. (See apps. I, II, and III for more details.)

Clinical investigators	Total	Bureau of Drugs	Bureau of Biologics
Number of investigators	172	153	19
Number in noncompliance with FDA requirements	67	54	13
Percent in noncompliance with FDA requirements	39	35	68

Sponsor/investigators	Total	Bureau of Drugs	Bureau of Biologics
Number of sponsor/ investigators	52	34	18
Number in noncompliance with FDA requirements	26	15	11
Percent in noncompliance with FDA requirements	50	44	61

Because failure rates of investigators subject to regulation by the Bureau of Drugs appeared much lower than those regulated by the Bureau of Biologics, we reexamined the 19 sponsor/investigator consent forms classified by the Bureau of Drugs as being "probably adequate" or "exemplary." Using Bureau of Drugs criteria, we found that 14 of the 19 forms were deficient and misclassified. In 4 of the

14 cases, the clinical investigator failed to obtain informed consent from some of his test subjects. And in the remaining 10 cases deficiencies in the forms included a failure to disclose the risks and benefits of the experimental drug and the alternative treatment available. Adjusting for these misclassifications, the Bureau of Drugs failure rate for sponsor/investigators increased from 44 to 85 percent. We did not review the consent forms of clinical investigators classified by the Bureau of Drugs to determine if similar misclassifications occurred.

Violations disclosed by the inspections included failure to obtain consent, use of forms containing exculpatory language, and other deficiencies in the forms used. FDA's summary of its inspection results identified the overall percentage failing to comply with consent requirements but not the frequency of each type of violation. Examples of each type of violation follow.

Failure to obtain informed consent

Informed consent is a basic way the FD&C Act and FDA regulations assure that patients are protected. The requirement of informed consent is intended to give test subjects a choice of whether they wish to participate in the new drug experiment and to provide information upon which to base such a choice. Yet these provisions are sometimes not met.

--An experimental drug used to treat whipworms was administered to mentally retarded children having IQs of about 35. FDA's inspection showed consent was not obtained. The clinical investigator and the IRC decided that obtaining consent from parents or guardians was unnecessary because they had previously authorized the use of medical, surgical, or dental procedures necessary to the child's general health and well-being. Such authorization, however, did not cover use of experimental drugs and was to include only instances in which reasonable attempts to obtain the consent of parents or guardians was unsuccessful. No attempt to contact parents or guardians was made.

--A radioactive drug was used in a study involving 37 elderly patients. The FDA inspector reported that written consent was not obtained because the sponsor/investigator was not aware of the requirement. The sponsor/investigator said that most patients used in his study were mentally incompetent, so the consent would have to have been obtained from a relative. He was not aware that this was permitted under FDA regulations.

Deficiencies in consent form

When written consent was obtained, FDA found that the information given test subjects was often inadequate. As illustrated by the following example, some consent forms were very general and provided little information.

The following is the wording of the complete form used to obtain the consent of 19 patients for testing a diagnostic drug to detect gallbladder problems that did not show up in X-ray or gastrointestinal studies.

> "The nature of the drug [drug name] and its complications has been explained to me by [the doctor]. I understand this drug is not widely used at this time nor has it been officially approved by the Food and Drug Administration."

This form, rated by Bureau of Drugs as needing improvement, does not show that the drug is experimental. Neither does it meet FDA criteria for providing a fair explanation of the procedures to be followed; description of discomforts, risks, and benefits; and disclosure of alternative diagnostic procedures available.

Other forms obtained during FDA inspections were deficient in that they:

--Repeated the basic elements of consent rather than using these elements as guidelines for providing a concrete description of what the drug is, why it is being given, the individual dose, the route, how often and for how long it will be given, the known hazards of it and the discomforts involved, what potential benefits may be gained, and what alternative forms of therapy are available.

--Failed to give the subject a fair explanation of such pertinent information as what or how long additional tests or examinations would be required in connection with the use of the experimental drug.

--Failed to inform the subject of the results of pertinent animal and/or previous clinical studies with the drug to enable the subject to exercise free choice.

--Failed to state what steps would be taken to prevent or minimize the possible risks and hazards associated with the drug.

--Failed to use simple language rather than medical terminology in explaining the details of the proposed study.

--Failed to tell the subjects that some would serve as control subjects who would receive either a placebo substance or an alternative drug rather than the investigational new drug under study.

Consent forms containing exculpatory language

Many consent forms contained exculpatory language intended to release everyone connected with the study from legal liability, even though this was contrary to FDA policy. Following are typical examples of the language used.

The consent form used for inmates in a State prison read:

"I * * *, hereby fully and forever release, acquit and discharge the * * * [State, State prison system, the prison] and all their agents, officers, and employees, the investigators for this project, and the * * * [research institution] together with their officers and employees, from any and all liability which may accrue on account of any and all claims or cause of action which in any way arise from my participation in a research project known as: * * *"

In a study to evaluate the tranquilizing effects of an experimental drug on patients with psychiatric disorders, the following consent form was used.

RELEASE OF ALL CLAIMS

"WHEREAS [patient's name] of * * *, is desirous of participation in the * * * Program conducted by research investigators of the * * * [clinic and/or * * * hospital] and has been advised with [sic] such investigators relative to such program:

"The undersigned consents to all facets of the * * * Program, and hereby holds harmless and releases from all liability * * * Hospital, all personnel of * * * Hospital, or any other hospital facilities utilized, as well as the attending physician, photographers, and all others connected with and/or participating in the conduct of the above mentioned program, from all claims related to such Program."

And finally, in a study involving immunized blood donor volunteers, the following exculpatory language was included in the consent form.

> "In consideration of the sum of $5.00 paid to me for my services as a donor, receipt of which is acknowledged, I agree to assume all of the direct and indirect risks involved, including personal injuries which I may sustain, and I RELEASE [name of corporation] its employees and the physician named above from all liability due to the injury or damage in connection with or resulting from this procedure."

CONFUSING AND MISINTERPRETED CONSENT REGULATIONS

FDA regulations are in certain respects confusing and subject to misinterpretation; thus they have contributed, in part, to the deficiencies in the consent obtained.

Elements of consent

Commenting on the importance of consent in protecting test subjects, the Commissioner of FDA, in his testimony of February 5, 1973, before the Subcommittee on Monopoly, Senate Select Committee on Small Business, said:

> "[The 1962 Amendments to the FD&C Act were] enacted specifically to protect the public, including those people who may participate in drug investigations.
>
> "The Act specifically provides that the investigator obtain the consent of such patients before they are included in any new drug investigation. The FDA has promulgated regulations which specify the substance of informed patient consent."

Within FDA there are varying interpretations on whether the regulations "specify the substance of informed patient consent." In 1974 HEW published regulations for the guidance of NIH grantees which provided new guidelines describing the elements of consent. Since then, when criticizing sponsors and clinical investigators for using consent forms that do not contain the basic elements of consent, the Bureau of Drugs has cited the HEW guidelines rather than FDA regulations because the elements of consent are more clearly described.

In addition to the four elements required by FDA regulations shown on page 31, the HEW guidelines require that persons obtaining consent include an offer to answer any questions about the procedures and a statement that the participant is free to withdraw from the study at any time. In its December 30, 1974, letter to a sponsor/investigator, the Bureau of Drugs stated:

> "We would note that the patient consent form dated November 3, 1974, on your letterhead stationery * * *, needs improvement. We are enclosing a recent Federal Register reprint which delineates the necessary elements of consent. While these regulations apply only to [HEW] supported research, they reflect our position relative to the obtainment of consent in all drug research studies."

The Bureau of Biologics also used the 1974 HEW guidelines rather than FDA regulations to determine the adequacy of consent forms obtained during inspections of clinical investigators. The Director, IND Staff, Bureau of Biologics, considered the FDA regulations on the substance of informed consent to be vague and unenforceable.

On the basis of a Bureau of Biologics evaluation of inspections made for us, the Director, IND Staff, stated that:

> "The content and quality of the majority of patient consent forms * * * were poor or incomplete. However; in the absence of having the essential elements of a patient consent form concretely stated in the regulations, it is not feasible to cite these deficiencies as deviations from the regulations."

As a result, the Bureau of Biologics did not comment to the clinical investigators on the poor quality or incomplete content of consent forms.

We questioned the position of the Director, IND Staff, that FDA regulations were vague about the basic elements of consent and requested him to reexamine FDA's regulations. Upon reexamination he found that four of the six basic elements from the 1974 HEW guidelines were explicitly stated in FDA regulations. The Director said he had never before made a point-by-point comparison of FDA's consent regulations with HEW's basic elements. He said he was surprised and enlightened to learn that such concrete elements were spelled out in FDA regulations.

As a result of the reexamination, the Bureau of Biologics sent letters to 20 clinical investigators and required them to revise their deficient consent forms to make them conform to FDA regulations.

Submission of consent forms to FDA

The Bureau of Biologics and the Bureau of Drugs did not agree on FDA's authority to require sponsors to submit consent forms to be used during a clinical investigation for FDA review and approval.

Since June 1972 the Bureau of Biologics has obtained consent forms as a part of the IND application. The IND Staff reviewed the forms and suggested improvements to the sponsors.

The Bureau of Drugs, however, does not obtain consent forms at the time IND applications are approved. As a result the Acting Deputy Director, Bureau of Drugs, stated "We don't know what, in fact, patients are told or, in the case of written consent, what they sign." The Director of the Bureau explained that the Bureau did not obtain consent forms because:

> "It is not required in the regulations. If it were, we could do it across the board. Some reviewers on their own had been requesting them from the firms routinely. Firms were having troubles with their investigators over this, so they complained to us. Since this was discriminatory, I told the directors that if we wanted it done, we should change the regulations. Until then, the reviewers should abide by the regulations, unless there is a specific (non-routine) reason for requesting consent forms."

Obtaining oral consent in phase III tests

Confusion also persists about whether FDA's regulations permit clinical investigators to routinely obtain oral consent during phase III testing. Although written consent is clearly required for phase I and II testing, the regulations (as cited on pp. 31 and 32) are not explicit for phase III. As a result, FDA officials as well as sponsors have made different interpretations. For example, the Acting Deputy Director, Bureau of Drugs, in a memorandum to the Director dated November 30, 1972, stated:

"Our own regulations require written consent except for unusual circumstances, however, there has been a widespread misinterpretation of these regulations by investigators and drug firms whereby they are obtaining written consent in Phases I and II and oral in Phase III."

The Director, Bureau of Drugs, told us that written consent in phase III is preferable but not necessary. The Director, Scientific Investigations Staff, Bureau of Drugs, however, told us that oral consent may be obtained only in an exceptional case and FDA's regulations indicate written consent should be obtained as a rule during phase III.

The Director, IND Staff, Bureau of Biologics, told us that he interprets FDA's regulations as recommending written consent during phase III but allowing oral consent if documented in the patient's record.

FDA officials said the regulations were deliberately made ambiguous when issued. When FDA issued its proposed regulations in 1966, it required written consent in phase III. However, the Assistant to the Director for Regulatory Affairs, Bureau of Drugs, told us that this proposal caused a furor in the medical profession because doctors believed it would hinder drug research. So, when FDA issued the final regulation in 1967, it changed the wording of the requirement.

Although FDA recognizes that obtaining informed patient consent is a principal means of protecting human test subjects and acknowledges that its consent regulations are ambiguous, it has not revised those regulations.

CONCLUSIONS

Patient consent, required by law and recognized by FDA as a principal means of protecting test subjects, has not always been obtained as required. FDA has not aggressively pursued its responsibility to insure that patient consent is obtained. As a result, many test subjects are inadequately informed of their participation in clinical investigations of new drugs.

FDA's failure to take more aggressive steps to insure that informed consent if obtained is related, to some extent, to (1) inadequately defined elements of consent in FDA's regulations, (2) varying interpretations of FDA regulations regarding the requirement for written versus oral consent during phase III studies, and (3) the differing views over FDA's right to routinely review consent forms before studies begin. Also, as discussed in chapter 2, we believe problems in

obtaining consent are related to FDA's inadequate monitoring and enforcement of compliance with this requirement.

To eliminate the misunderstanding regarding requirements for obtaining consent, we believe FDA should revise its regulations for obtaining consent so that FDA personnel, sponsors, and clinical investigators will clearly understand what is required and FDA personnel can effectively and consistently enforce the requirements.

Oral consent in phase III in some cases may be justified. However, allowing oral consent as a rule in phase III diminishes FDA's ability to insure that proper consent is obtained because FDA has no way of knowing what the patient is told.

We recognize that obtaining written consent does not guarantee truly informed consent. That depends on the test subjects' ability to understand and comprehend the nature of what they are consenting to, as well as what they are told by the clinical investigator. We believe, however, that requiring written consent as a rule in all phases of clinical investigations--using a document that fully describes the pertinent study details--will greatly increase the likelihood that truly informed consent is obtained. Also, requiring that consent forms be submitted for FDA review and approval would enhance FDA's ability to insure that the requirement to obtain consent serves its purpose of protecting human test subjects.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to revise FDA regulations to:

--Conform to the elements of consent contained in HEW guidelines.

--Clearly require that written consent be obtained as a rule in phase III trials of clinical investigations. Exceptions allowing oral consent in phase III trials should be permitted only after obtaining FDA approval.

--Require the submission of consent forms for FDA review and approval before initiating the clinical investigation.

AGENCY COMMENTS

HEW said that, in the evolution of public awareness and concern for the protection of human subjects, FDA continues to review and upgrade its regulations in an attempt to provide

guidance in the negotiation of informed consent. HEW said that the concept of negotiating informed consent with a research subject has been evolving rapidly and believes that our recommendations focus on narrow aspects of the negotiation process. HEW explained that, when the FD&C Act established a requirement for informed consent in 1962, FDA issued its interpretations of how consent is to be obtained, based in part on its own experience and in part on expert advice. HEW noted that its 1974 regulations differed from FDA's most recent regulation (1967) with respect to elements of consent, documentation of consent, and prior approval of consent forms.

HEW said that:

> "Not all of these differences reflect simple policy decisions; the FD&C Act precludes mandatory submission of reports by investigators to FDA; consent is not required in every situation; the cost of compliance with requirements is not necessarily paid out of HEW grant or contract funds. Nor is the merit of some of the different requirements established; for example, prior approval of consent forms may not be as cost-effective as clearly defined requirements for such forms. The HEW regulations do not, therefore, represent definitive rules applicable to all situations, nor has any such code been yet devised. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research is currently studying subject consent, particularly as it relates to persons in unique groups such as prisoners, the mentally disabled and children. The Commission is due to make recommendations to the Secretary of HEW early in 1977."

HEW does not assume that mechanical requirements will guarantee informed consent but does believe that meaningful standards can contribute toward that goal. Accordingly, HEW said FDA would propose new regulations dealing with the elements of information essential for obtaining consent; whether oral consent is ever acceptable and, if so, under what circumstances; and what consent forms must, and must not, contain. These regulations will consider the National Commission's evaluation of current HEW and FDA regulations, its recommendations for change, the need for consistency in all departmental policies, FDA's legislative authority, and the cost-effectiveness of administrative review of documents and procedures to be used in individual studies to obtain informed consent.

CHAPTER 4

NEED TO STRENGTHEN INDEPENDENT THIRD-PARTY REVIEW

In addition to informed patient consent, FDA considers an independent review of clinical investigations by an IRC as an important means of protecting human test subjects. Beginning in April 1971 FDA required the sponsor to assure that an IRC would oversee all investigational new drug studies conducted on persons confined to such institutions as hospitals, nursing homes, prisons, and homes for the mentally retarded. Because such persons may be more vulnerable to abuse or exploitation by research projects than the general population, FDA believes special protection for them is warranted.

IRCs are intended to provide added safeguards for institutionalized test subjects by insuring that the

--rights and welfare of human subjects are protected,

--methods used to obtain informed consent are adequate and appropriate, and

--risks are outweighed by the potential benefits to the subjects or by the importance of the knowledge to be obtained.

FDA regulations require that IRC members have varying backgrounds and be competent to judge the acceptability of a study. The IRC is responsible for

--initially reviewing and approving the proposed clinical study;

--conducting continuing reviews at intervals appropriate to the degree of risk but not exceeding a year; and

--maintaining adequate documentation, which must be available to FDA upon request, on committee activities and on the information provided test subjects in obtaining consent.

FDA regulations state that, in addition to the sponsor's continuing responsibility to monitor the study, FDA will periodically investigate institutions to determine whether the IRCs are operating in accord with the sponsor's assurances. We found, however, that FDA made only a limited number of

IRC inspections. And the inspection results showed that the protection intended for institutionalized test subjects was not provided because IRCs were not adequately reviewing new drug studies.

FDA LACKS INFORMATION ON IRCS FOR INSPECTION PLANNING

FDA does not require sponsors or clinical investigators to furnish it with information identifying IRCs used in their clinical investigations. As a result, FDA does not have information on the number and locations of IRCs for planning IRC inspections, and FDA has inspected relatively few IRCs. As of October 1974, the Bureau of Drugs had inspected 25 IRCs since such inspections were first required in 1971. According to the Bureau's Director, Scientific Investigations Staff, some IRCs reviewed were selected from a list furnished by medical officers in the Bureau. Others were inspected because of adverse publicity or in connection with an inspection of a clinical investigator under another inspection program.

The Bureau of Biologics had never inspected an IRC and was not aware of the inspections provided for in the regulations.

National Institutes of Health records show that about 540 institutions receiving NIH research grants have IRCs and, although others exist, FDA does not know how many. Without knowing the universe of IRCs, FDA cannot make an inspection effort that would insure representative coverage and enable it to evaluate overall IRC performance.

During each of fiscal years 1976 and 1977, the Bureau of Drugs plans to inspect 24 IRCs. The Director said IRCs will be selected for inspection when they are identified under other inspection programs.

Rather than leaving the identification and selection of IRCs to chance, FDA should develop and maintain a complete, current list of IRCs. In addition to providing the basic management data FDA needs to help fulfill its IRC regulatory responsibilities, the data base would permit the selection of random inspection samples. This would enable FDA to project its inspection findings to the universe of IRCs in evaluating IRC compliance while efficiently using its limited inspection resources.

Developing a system for obtaining and maintaining an adequate data base for inspection sampling is especially important, considering FDA's plans to require IRC review

for studies involving noninstitutionalized patients. When the requirement for involvement of IRCs was published in 1971, FDA recognized that noninstitutionalized test subjects may be as much at risk as the institutionalized and should, therefore, be given the same opportunity for the added protection expected from independent third-party review. FDA is still considering IRCs for noninstitutionalized patients. Such a requirement, if adopted, would mean that all clinical investigations would be subject to IRC review.

INDEPENDENT REVIEW BY IRCS INEFFECTIVE

The Director of the Bureau of Drugs described the IRC's importance and FDA's reliance on it when he stated:

> "The patients' first line of defense on ethical issues and the second line of defense on medical issues is the IRC. FDA's review of INDs is only a tertiary defense and should be directed mainly at only those things that IRCs aren't good at--the design of protocols, the interpretation of animal data, and manufacturing controls data."

Unfortunately, FDA inspections of IRCs disclosed numerous deficiencies in their performance, thus reducing their effectiveness in protecting test subjects.

The 25 IRCs the Bureau of Drugs inspected were responsible for reviewing studies in the following types of institutions.

Prisons	11
Mental institutions	8
Children's hospitals	3
University research centers	2
Nursing home	1
	25

FDA had scheduled inspections at two other institutions--a nursing home and a county jail--but found that the IRCs had not been established as required. Of the 25 IRCs FDA inspected, no deficiencies were found in two cases involving children's hospitals. In the remaining 23 inspections, FDA found deficiencies as shown on the following page.

Type of institution	IRC deficiencies identified by FDA inspections: Approved inadequate consent form	Lacked continuing review	Failed to maintain records	Lacked varying background
Prisons	9	6	6	8
Mental institutions	3	1	2	5
University research centers	0	0	0	2
Nursing home	0	0	0	1
Children's hospital	1	1	1	1
	13	8	9	17

In addition, the inspection reports noted that IRCs in three prisons were paid for their services by the sponsor or clinical investigator.

Failure to insure adequate consent forms used

To provide the special protection it believes is warranted, FDA requires IRCs to insure that the methods used to obtain informed consent of institutionalized persons are adequate and appropriate. This includes an IRC review of consent forms to insure that the form contains the elements of consent and does not contain exculpatory language.

FDA found that 13 of 25 IRCs inspected had approved faulty consent forms. In 11 of the 13 cases, exculpatory language was used. In eight instances the form failed to advise test subjects that they were free to withdraw from the experiment at any time--a point that seems important considering the potential for abuse and exploitation of institutionalized test subjects.

Failure to provide continuing review

FDA requires IRCs to review the progress of drug studies at least annually--and more frequently if the IRC determines the risks to test subjects warrant it--to insure the research is being conducted according to the IRC's understanding and recommendations. The clinical investigator is to give the IRC all information on the study necessary for the IRC's complete review. Also, the clinical investigator is to report to the IRC any emergent problems, serious adverse reactions, or proposed procedural changes that may affect the status

of the study. No procedural changes are to be made without IRC approval expect when necessary to eliminate apparent immediate hazards.

FDA found that 8 of the 25 IRCs inspected did not review the investigational drug study after initial approval. FDA's inspection reports contained the following observations.

--The IRC for one prison was not aware of FDA's regulations governing IRCs. It did not make a continuing review.

--The IRC for another prison did not receive information on the results of ongoing or completed studies. The prison warden said his administrative assistant constantly monitored the study and would report any problems to him. The assistant was paid by the firm conducting the studies, a possible conflict-of-interest situation.

--Another prison IRC never reviewed ongoing studies or final reports.

The following examples illustrate the effects of IRC failure to review ongoing studies. In these examples, FDA inspected both an IRC and the clinical investigators the IRC was to monitor.

IRC A

In June 1974 FDA inspected IRC A, which was responsible for reviewing investigational drug testing at a State institution for the mentally retarded. Children at the institution were used in a study of an investigational drug for treating pinworms and whipworms.

FDA found that the IRC had not assured itself that the clinical investigator obtained informed consent. Also, the IRC had no provision for reviewing studies during their execution and no policy to insure that a clinical investigator would report emergent problems or procedural changes in the study as required by FDA regulations.

FDA's inspection of the clinical investigator showed that he had not complied with FDA requirements for informed consent, drug accountability, and reporting. In addition, the investigator deviated from the protocol and maintained only limited control over the study, with portions conducted by nurses in two separate units without his supervision.

IRC B

In January 1974 FDA responsed to a congressional inquiry to inspect the activities of IRC B, which was responsible for clinical investigations at a mental institution. During its inspection, FDA reviewed the IRC's actions on six investigational drug studies and found that the IRC had failed to adequately review studies in general and had approved consent forms containing exculpatory language.

One study involved a marketed drug that was being tested for use in the treatment of chronic brain syndrome--a condition for which the drug was not approved for market. Test subjects were elderly patients having psychotic symptoms and/or other behavioral difficulties. FDA's review showed the study was submitted to the IRC for review, but, contrary to FDA regulations, the IRC did not review it because the chairman did not believe that a study involving a marketed drug required IRC approval. Consent forms had been obtained from patients who, according to FDA, were not capable of giving informed consent because of their diminished intellectual performance and low level of consciousness.

Although the one patient death that occurred could not be established as drug related, FDA concluded that the use of the patient in the study appeared to have been ill advised because the patient was unable to communicate and had a history of hemiplegia (paralysis of one side of the body) and fluctuations in blood pressure. Therefore, including the patient in the study seemed to provide little useful information and may have placed the subject at unnecessary risk.

FDA inspectors were informed that this IRC was generally concerned only with patients' rights in the studies it reviewed and that adverse reactions and deaths might not have been reported to it. In its letter to the institution, FDA pointed out that "* * * If this is the case, we would draw your attention to the fact that continuing review is considered to be an essential function of institutional review committees * * *."

Failure to maintain records

To provide a basis for evaluating IRC performance and compliance with FDA regulations, FDA requires that IRCs (1) record their recommendations concerning the clinical study, (2) document their discussions of substantive issues and how they were resolved, and (3) prepare reports on their ongoing reviews of the clinical investigation. FDA found that, of the 25 IRCs inspected, 5 kept no minutes of

meetings, records, or documents and 4 kept records that were incomplete or extremely sketchy.

IRC members lack diverse backgrounds

IRCs must have not only broad competence to understand the nature of the study but also other competencies needed to judge its acceptability in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Accordingly, FDA regulations state that IRCs must be composed of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to insure complete and adequate review of the research project.

As shown below, 17 of the 25 IRCs inspected did not include persons from one or more of the backgrounds mentioned by FDA regulations.

Composition of IRCs Inspected
(X indicates absence)

Type of institution	Clergy	Lawyers	Laymen	Scientists
Prisons				
1.	X		X	
2.	X	X	X	
3.		X		
4.	X			
5.			X	
6.	X		X	
7.			X	
8.	X	X	X	X
Mental institutions				
9.	X	X		
10.	X	X	X	
11.			X	
12.	X			
13.	X			
Other				
14. University research center			X	
15. University research center	X	X		
16. Nursing home		X		
17. Children's hospital	X	X		
Total	11	8	9	1

Payment of IRC members

FDA believes an IRC should be independent of the drug firm sponsoring and the individual performing the clinical investigation. The inspection reports stated that 3 of the 25 IRCs inspected received payment for their services from the sponsor or clinical investigator. At one prison the clinical investigator paid the IRC chairman $4,000 and each member of the committee $2,000 per year. At two other prisons IRC members were paid an unspecified amount by the sponsor or investigator. FDA regulations do not prohibit such payments.

FDA's inspections do not show that the payments influenced the IRCs' performance. The inspection results show, however, that the IRCs did not comply with FDA requirements. For example, in the case in which the IRC chairman received $4,000 and each member $2,000 per year, the IRC approved an inadequate consent form and failed to make a continuing review of the study. The IRCs whose members were paid an unspecified amount by the sponsors or investigator approved an inadequate consent form, did not review the study as it progressed, and failed to maintain any records of its activities.

FDA's Associate Chief Counsel for Drugs said that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has contracted for a study of IRCs and that at the conclusion of the study FDA will consider the need for regulations dealing with several issues concerning IRCs, including whether IRC members may be paid and, if so, by whom.

CONCLUSIONS

FDA considers independent third-party review an important safeguard for protecting the health, safety, and welfare of institutionalized test subjects--those often incapable of protecting themselves.

Although FDA in its regulations stated its intent to inspect IRCs periodically, it does not know how many IRCs exist or where they are located. Without such information, FDA is unable to pursue an effective inspection program that would insure representative coverage and enable it to evaluate overall IRC performance. FDA should require sponsors to provide information on the IRCs that are used in clinical investigations so that it can develop and maintain a complete list of IRCs.

FDA inspections of a limited number of IRCs indicate that IRCs are not fulfilling their responsibilities and that FDA should strengthen its regulation of IRCs. Because the FDA inspections revealed many deficiencies by IRCs, we believe the sponsor should be required to submit information on the IRC's composition and a signed statement from the IRC indicating its awareness of and willingness to fulfill its responsibility. Such a requirement would better assure FDA that a properly constituted IRC would monitor the study.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to:

--Require sponsors to furnish information on the IRC composition and location.

--Develop and maintain a list of IRCs, their location, and their composition.

--Require sponsors to submit to FDA a signed statement from the IRC indicating its awareness of and willingness to fulfill its responsibility as an IRC.

--Emphasize to FDA bureaus the importance of the requirement for periodically inspecting IRCs.

AGENCY COMMENTS

HEW stated that the new regulations it intends to issue will require the sponsor to assure that investigators submit proposed protocols to the IRC and that the IRC has approved the protocols. The sponsor will also be required to assure that committee composition is in accordance with established guidelines and that the committee will be responsible for continuing review and approval of the investigational new drug study. HEW added that the forms for reporting this information have been revised and will be in use shortly.

Accordingly, HEW pointed out that FDA will be routinely receiving information on the IRC composition. Compiling the information into a centralized list, however, would not be very useful to the agency given the current level of monitoring resources. The information that is received on IRCs will become a permanent part of the IND files and will therefore be readily available for use in planning, directing, and making inspections of IRCs.

With regard to periodic inspections of IRCs, HEW said that such a periodic inspection program cannot be created by simply emphasizing the need for these inspections. HEW noted that the underlying problem is one of limited resources in the face of competing priorities. According to HEW, although FDA plans to inspect a limited number of IRCs to the extent that resources permit, additional inspections of IRCs would be made at the expense of clinical investigator and sponsor inspections. This trade-off, HEW said, must be carefully considered in light of anticipated benefits.

To help FDA strengthen its monitoring activities, on April 22, 1976, the President asked the Congress for an additional $16.3 million in a fiscal year 1977 budget amendment to increase efforts in certain FDA program areas, including monitoring preclinical and clinical testing of new drug products. The additional funding, if provided, should permit FDA to increase its IRC inspections with less impact on its other inspection activities.

CHAPTER 5

NEED FOR CLARIFYING FDA'S AUTHORITY OVER CLINICAL INVESTIGATIONS SPONSORED BY FEDERAL AGENCIES

Clinical investigations are sponsored by Federal agencies as well as drug firms and private physicians. At the time of our field work, the primary Federal drug sponsors were the Department of Defense (DOD) and NIH. DOD was sponsoring 53 clinical investigations, and NIH was sponsoring 222. A question exists as to whether FDA's authority to regulate clinical investigations of experimental drugs under the FD&C Act extends to such investigations sponsored by other Federal agencies.

Section 505(a) of the FD&C Act generally prohibits a person from introducing into interstate commerce any new drug without FDA approval. A "person" is defined in section 201(e) of the act as an "individual, partnership, corporation, and association" and does not specifically include Federal agencies and departments.

Section 505(i) authorizes experimentation with investigational drugs without the approval required under section 505(a) and empowers FDA to issue regulations prescribing the conditions under which the IND exemption will be granted. Section 505(i) and the regulations issued pursuant to it also apply only to persons, and since the term "person" as defined in the act does not specifically include Federal agencies or departments, experimentation with investigational drugs by Federal agencies and departments may not be subject to FDA regulation under section 505(i).

FDA had not inspected clinical investigations sponsored by DOD or NIH until we requested that it inspect some. The inspections showed generally the same types of deficiencies as were found in FDA inspections of non-federally-sponsored studies. (See ch. 2.) Also, in some cases, FDA waived requirements of its regulations. Further, the Bureau of Biologics did not attempt to regulate federally sponsored investigations because it did not believe the FD&C Act provided regulatory authority over other Federal agencies.

DOD-SPONSORED CLINICAL INVESTIGATIONS

In 1962 the medical departments of the DOD services (particularly the Army) became concerned that tighter FDA

control resulting from the 1962 Kefauver-Harris Amendments would impede the search for new drugs needed for the Nation's defense. DOD believed it had unique medical responsibilities affecting the Nation's security and that the Commissioner of FDA had no background in evaluating the potential military value of a drug as compared with the degree of risk involved in clinical trials. DOD thus believed it could exercise better control over clinical investigations it sponsored.

In 1964 HEW and DOD entered into an agreement, made formal by a memorandum of understanding, on the use of investigational drugs. Essentially, DOD was not required to file a formal IND application for clinical investigations classified for reasons of national security. The proposed tests for such classified studies were to be reviewed and approved by a DOD review board and surgeon general. The review boards were to insure adequate protection of human subjects through competent review of the research protocols by qualified professionals. All classified testing was to be discussed periodically with FDA personnel having security clearances.

DOD classified drug tests

An official of the Office of the Surgeon General of the Army told us that since the 1964 agreement the Army had not conducted any classified clinical investigations of new drugs. However, as a result of the Rockefeller Commission's investigation of Central Intelligence Agency activities, it was disclosed that the Department of the Army had conducted secret drug tests using LSD and other hallucinogens. These tests were conducted at Edgewood Arsenal, Maryland, and elsewhere.

The House Armed Services Subcommittee on Investigations held hearings on the secret drug tests. Also, joint hearings were held by the Subcommittee on Health of the Senate Labor and Public Welfare Committee and the Subcommittee on Administrative Practice and Procedure of the Senate Judiciary Committee. Because of these investigations we did not pursue the matter further. However, the testimony showed that many of the FDA regulations for protecting patients were not followed in the secret tests. Test subjects in some cases were not told they were being given the drug until after it was administered, and continuing adverse effects resulted from the drugs.

The FDA Commissioner testified that FDA's regulation and surveillance of these classified tests was minimal. Although the 1964 memorandum of understanding called for

HEW and DOD to periodically meet to discuss classified tests, during the first 10 years of the understanding only four such meetings were held. Of these, only two, according to the Commissioner, provided any exchange of significant information on test results. Thus, FDA did not exercise surveillance over the classified tests and DOD, as indicated by testimony before congressional subcommittees, did not observe FDA's regulations for patient protection.

The HEW and DOD memorandum of understanding was revised in 1974. (See app. IV.) It still exempts from FDA regulation those clinical investigations classified for reasons of national security. The only change in this regard is that DOD is required to discuss its classified investigations with FDA personnel having security clearance on a "frequent" basis, whereas the original agreement required only "periodic" discussions. The agreement does not specify the need to obtain consent from test subjects. However, the DOD appropriation acts for fiscal years 1973, 1974, 1975, and 1976 impose such a requirement (Public Laws 92-570, 93-238, 93-437, and 94-212).

DOD unclassified drug tests

For unclassified drug studies, the 1964 agreement specified that DOD would submit to FDA an IND application consisting of copies of (1) the request for approval submitted to the DOD review board, (2) the review board's evaluation and approval, and (3) the DOD surgeon general's approval. These submissions were sometimes much briefer and less specific than normal filings and did not contain the clinical investigator's signed assurance that he or she understood his or her responsibilities as specified in FDA regulations. FDA was to handle such submissions in the same way as any other IND application.

According to the revised agreement, unclassified clinical investigations would be subject to all new drug regulations and normal IND filing requirements.

Because FDA had never inspected DOD-sponsored clinical investigations, in 1974 we asked FDA to inspect six Army-sponsored 1/ clinical investigations being conducted in five locations. About 1,175 test subjects participated in the 6 studies. FDA made inspections at

---

1/Neither the Navy nor the Air Force had active IND exemptions at the time of our review. However, FDA officials stated that, although their experience with the other services as sponsors was very limited, it was "less satisfactory" than with the Army.

--the U.S. Army Research Institute of Environmental Medicine, Natick, Massachusetts, which was testing drugs;

--the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland, which was testing vaccines;

--Fort Ord, California, a combat training center which was testing vaccines on recruits;

--Stateville Penitentiary, Joliet, Illinois, where an Army contractor was testing antimalarial drugs on prisoners; and

--Walter Reed General Hospital, Washington, D.C., which was testing an investigational radiopharmaceutical.

The inspection results show that conformance with FDA regulations ranged from good to very poor and was generally similar to conformance by civilian clinical investigators. Nonconformance with FDA regulations included:

--Inadequate drug accountability (four locations).

--Failure to report protocol changes of varying degrees of significance, such as a new coinvestigator, not using a control group for part of a study, starting phase II with a dosage 100 percent higher than specified in the protocol, use of 50 percent greater radioactivity than specified, and use of children as subjects when not specified (four locations).

--Beginning and completing tests before submitting the IND application to FDA (two locations).

--Failure to report change in the drug source (one location).

--Failure to submit progress reports to FDA when required (three locations).

--Investigator's participation on the local institutional review committee--he voted for approval of his study (one location).

--Failure to note in patient's records that oral consent was obtained (one location).

--Failure to obtain consent (one location).

Routine use of investigational drugs by DOD

The military services have routinely used four experimental drugs--three vaccines and an antimalarial drug that has an approved new drug application for treatment of leprosy but not for malaria. Routine use refers to administering an unapproved drug or vaccine--usually on a large scale--as if it were not an experimental drug but as if FDA had approved it for marketing. (The informed consent of the recipient is not obtained.) FDA was aware of such routine use but did not object to the Army or the other services. The drugs were routinely administered to over 2 million servicemen. FDA was not kept advised of DOD's experiences with the drugs.

Adenovirus type 4 and type 7--These are major causes of acute respiratory disease, a problem at basic combat training centers. The Army sponsored development of three vaccines against these adenoviruses, and on February 2, 1970, the Surgeon General of the Army authorized routine use of these vaccines. The vaccines were tested on about 10,000 recruits at basic training centers, and the Army estimated that as of May 1974 the vaccine had been routinely administered to from 500,000 to 750,000 recruits. Such use was continuing.

On December 8, 1970, Army and Bureau of Biologics (then the Division of Biologics Standards, NIH) personnel informally met to discuss the potential problem of vaccine suppliers balking at supplying unlicensed vaccines for routine use and to agree on recordkeeping and reporting requirements, since the Army no longer considered the vaccines investigational.

Army personnel agreed to develop a policy pertaining to their recordkeeping and reporting practices and to advise the Bureau of their plan. Neither the Army nor FDA could find evidence that this had been done. Representatives of both agencies conjecture that a plan was never developed.

Dapsone--In June 1966, after clinical investigations with Dapsone (an approved drug for the treatment of leprosy) involving about 2,550 test subjects indicated it to be an effective antimalarial drug, the Surgeon General of the Army requested approval of the FDA Commissioner to use Dapsone routinely. The use was intended for combat forces and ancillary personnel in sections of Vietnam where malaria strains resistant to the existing antimalarial drugs were present.

The Commissioner replied that, in the absence of more data on the toxicity of Dapsone to man, such a request would

not be approved had it come from civilian quarters. He said, however, that FDA would not object if the Surgeon General considered the use of Dapsone to be in the interest of national security. Essentially, the Commissioner's only requirement was that FDA be sent pertinent reports on the use of the drug.

Dapsone was given to about 1,600,000 people as an antimalarial under this special authorization. However, the Army did not keep FDA currently advised of new developments in the use of Dapsone. The first progress report was not submitted until October 1968, over 2 years after the routine was began and after FDA notified the Army that a report was due. Army records show the report consisted of a reprint of a 2-year-old article on the use of Dapsone written by an Army doctor.

Nothing more was submitted until February 1970, despite the Army's identification early in 1969 of two potential adverse reactions to Dapsone. One was the possibility that the drug could impair the judgment of combat forces or diminish their physical stamina. The other reaction (agranulocytosis, affecting the blood and mucus membranes) resulted in the deaths of 8 of 16 soldiers during the first 10 months of 1969. The FDA medical officer responsible for monitoring the Dapsone study said the Army took all the necessary precautions--except promptly notifying FDA--when it noticed the adverse reactions. Although the Army was aware of the problem as early as May 1969, it did not advise FDA until February 17, 1970.

The Army later determined that Dapsone did not significantly affect the judgment and stamina of combat forces, except in such unusual situations as high-altitude flight in unpressurized compartments. The eight deaths associated with the drug were thought possibly to have been related to decomposition of the Dapsone before administration. The Army subsequently destroyed some of its old Dapsone supplies and altered the method of shipping Dapsone to minimize the threat of this problem.

The Army submitted its next progress report on the use of Dapsone in August 1972, 2-1/2 years later, despite two letters from FDA reminding the Army a report was overdue. From August 1972 until June 1974, no reports were submitted to FDA, despite a "reminder letter" in November 1973. The June 1974 report stated that, since the U.S. military involvement in Southeast Asia had ended, the Army Investigational Drug Review Board had withdrawn its approval for the use of Dapsone in routine malaria prophylaxis and recommended that all supplies of Dapsone be suspended from military issue and use.

FDA officials said no special safeguards or special procedures were established for monitoring DOD's use of Dapsone. FDA medical officers responsible for reviewing and monitoring the Dapsone IND exemption were not advised that the Army had been given special authorization to use Dapsone routinely. Therefore, the FDA personnel who were to receive the pertinent data from the Army were not aware of its significance or the importance of receiving it in a timely manner. In fact, the FDA medical officer responsible for the Dapsone IND exemption since 1971 was not aware of the special authorization until we discussed it with him in June 1974.

The memorandum of understanding as revised in October 1974 stipulates that when the unique requirements of the military dictate the extensive use in military personnel of drugs not yet approved by FDA, ad hoc review and approval of such use will be carried out jointly by DOD and FDA representatives.

NIH-SPONSORED CLINICAL INVESTIGATIONS

At our request, FDA inspected five clinical investigators of NIH-sponsored drugs. It made two investigations at the NIH campus, Bethesda, Maryland, and the others in Arizona, California, and Massachusetts. Twenty-five test subjects were involved in these studies.

Although the inspection results indicate consent was obtained from test subjects, the forms used in three of the five studies were general and did not contain all four elements required by FDA for informed consent. (See p. 31.) Two of these forms were standard NIH consent forms.

The inspections also revealed the following types of noncompliance with FDA's new drug regulations:

--Inadequate drug accountability (three locations).

--Continued administration of the drug after the study was formally discontinued (one location).

--Unreported protocol changes of varying degrees of significance, such as failure to perform all specified preliminary laboratory tests and use of a child as a subject when only adults were specified (two locations).

--Drugs administered before submitting an IND application to FDA (one location).

--Shipment of the drug to a coinvestigator without properly labeling it as an investigational drug (one location).

In a letter to one of the investigators, FDA expressed concern that he continued to administer the drug after discontinuation of the IND and that he informed the patients to "stop taking the pills and throw away the bottle" when they got an attack--negating all efforts at drug accountability. The letter referred to the deficiencies as being "in direct opposition to our Investigational Drug Regulation."

FDA REGULATION OR SELF-REGULATION OF FEDERAL SPONSORS

FDA's Associate Commissioner for Medical Affairs cited the following as valid reasons for FDA regulation of Federal agencies' clinical investigations of new drugs.

--FDA has the guidance of an existing act, the FD&C Act.

--FDA has issued implementing regulations.

--FDA has an established organization to perform the regulation.

These would have to be established by the Federal agencies if they are made self-regulating. Further:

--FDA has organizational independence.

--Subjects of drug experiments conducted by Federal agencies should receive the same protection as subjects of drug experiments conducted by private sponsors.

--Data derived from Federal agencies' drug experiments may be important to the public.

--FDA may have knowledge from other experiments on the same or related substances that may affect the appropriateness of the proposed study or otherwise affect (positively or negatively) the study, and this information may not otherwise be available to the sponsor.

According to the Associate Commissioner, FDA is not capable of evaluating the military benefits of the use of a drug as a weapon and therefore would not be able to make complete risk-benefit evaluations in such cases.

CONCLUSIONS

The question of the applicability of the FD&C Act to Federal agencies and departments is extremely important and needs to be clarified by the Congress because it affects not only drugs regulated by FDA but also other products covered by the act. In clarifying its intent regarding the regulation of Federal sponsors, the Congress should consider whether it wishes the test subjects in federally sponsored investigations to receive the same protection as participants in non-Federal studies--through independent review and FDA enforcement of the requirements and safeguards of the FD&C Act and FDA regulations and through FDA's drug knowledge and experience accumulated over many years.

RECOMMENDATION TO THE CONGRESS

We recommend that the Congress resolve the question of the applicability of the FD&C Act to Federal agencies and departments by clarifying its intent regarding the regulation of federally sponsored clinical investigations of new drugs.

RECOMMENDATION TO THE SECRETARY OF HEW

Pending resolution by the Congress of the question of the applicability of the FD&C Act to Federal agencies, we recommend that the Secretary direct the Commissioner of FDA, pursuant to the memorandum of understanding with DOD, to include the clinical investigations sponsored by DOD in its comprehensive plan for monitoring and evaluating clinical investigations, as recommended in chapter 2.

AGENCY COMMENTS

DOD concurred in our conclusions and recommendations pertaining directly to it. (See app. V.)

HEW said that, in many respects, the recommendation to the Secretary poses the same dilemma as the recommendation in chapter 4 concerning the periodic inspection of IRCs. Inspections of DOD-sponsored clinical investigations can only be accomplished at the expense of other monitoring activities. However, FDA will devote some coverage to DOD-sponsored investigations in the future, although the level of coverage will be influenced by overall program considerations.

CHAPTER 6

IMPROVED COORDINATION NEEDED BETWEEN BUREAU OF DRUGS AND BUREAU OF BIOLOGICS

Clinical investigations regulated by the Bureau of Drugs and the Bureau of Biologics are subject to the same safeguards and requirements of the FD&C Act and FDA regulations and frequently involve the same sponsors and investigators. Although these commonalities exist, we found little coordination between the two bureaus, thus hampering FDA's regulatory efforts.

NEED TO EXCHANGE INFORMATION ON INVESTIGATORS, SPONSORS, AND IRCS

The Bureau of Drugs and the Bureau of Biologics have not routinely exchanged information on their monitoring activities. The monitoring efforts of one bureau could profit from the experience of the other. The inspection findings on individual clinical investigators, sponsors, and IRCs should be brought to the attention of the other bureau because the same sponsors, investigators, and IRCs might be subject to regulation by both bureaus. Also, overall trends, weaknesses, or conclusions identified or reached by one bureau should be shared with the other so each can make appropriate adjustments to its monitoring efforts.

No mechanism exists, however, to insure such exchange of information. For example, the bureaus had not routinely exchanged information on the inspections discussed in chapter 2. Further, the Bureau of Biologics had disqualified 10 clinical investigators, the last in 1971. The Bureau of Drugs, however, was not informed of the disqualifications and accepted one as a clinical investigator after he had been disqualified by the Bureau of Biologics. The Bureau of Drugs had disqualified 16 investigators from 1964 through 1970 but did not inform the Bureau of Biologics until 1973. The Bureau of Drugs disqualified four investigators during 1975 but had not notified the Bureau of Biologics as of January 14, 1976.

The Director, Office of Compliance, Bureau of Biologics, acknowledged that a need exists to establish a liaison to insure that the bureaus exchange information. An official of the Scientific Investigations Staff, Bureau of Drugs, agreed, stating that the two bureaus' paths had not crossed much in the past. A contributing factor may be that the Bureau of Biologics did not join FDA until July 1, 1972. However, there has been little or no coordination since then. The Director, IND Staff, Bureau of Biologics, said he had only superficial knowledge of the Bureau of Drugs' activities.

NEED TO COORDINATE INSPECTION ACTIVITIES

The two bureaus had not coordinated the inspection coverage to eliminate duplication and insure efficient use of FDA's resources in their parallel monitoring. Although the Bureau of Drugs' comprehensive plan discussed on page 20 is supposed to provide for coordination of inspection coverage, that is one of the parts of the plan that has not yet been fully implemented. According to an official of the Scientific Investigations Staff, that section of the plan has been delayed pending development of guidelines for sponsors' monitoring efforts. The data on both bureaus' IND exemptions should be computerized.

In addition to inspection coverage, the two bureaus have not adequately coordinated the development of their inspection programs. The Bureau of Drugs, which has had more inspection experience than the Bureau of Biologics, revised its inspection program in 1975 to reflect lessons learned in prior inspections. However, the Bureau of Drugs has not given the Bureau of Biologics the benefit of its experience.

The official developing the first inspection program for the Bureau of Biologics said he tried in vain in January, April, July, and October 1974 to obtain information from the Bureau of Drugs on its efforts to develop an inspection program. He characterized the responses as vague with an apparent reluctance to be specific and said he got the impression little progress was being made. In December 1974 he was again unsuccessful in obtaining the information. The Bureau of Drugs began making inspections under its new program only a few months later.

When the Bureau of Biologics finally completed its inspection program, the Bureau of Drugs official said it was too bad the Bureau of Biologics had patterned its program after the Bureau of Drugs old program. He said experience had shown a number of weaknesses needing correction. The Bureau of Biologics official said it was too late to change the program and that it would be used beginning in about December 1975.

The Director, IND Staff, Bureau of Biologics, said the bureaus had little or no coordination since the Bureau of Biologics joined FDA. He said that until our review he was not aware of the availability of FDA inspectors. Lacking this knowledge, he had no inspections made because he lacked sufficient manpower. Both he and the Director of the Bureau agreed that the inspection activities of the Bureau of Drugs and the Bureau of Biologics should be coordinated.

NEED FOR MORE UNIFORM TREATMENT OF SPONSORS AND CLINICAL INVESTIGATORS

The two bureaus differ in the requirements they impose on sponsors and clinical investigators for obtaining oral consent in phase III trials. The Bureau of Drugs is satisfied if the investigator notes in the patient records that oral consent was obtained. The Bureau of Biologics, however, after reviewing the results of the inspections we requested, decided to ask sponsors to submit--when oral consent is to be obtained--(1) an explanation from the investigator of why he or she has decided that it is necessary or preferable to obtain other than written consent and (2) a written copy of the statements that will be made to obtain oral consent.

For written consent (see p. 38), the Bureau of Biologics requests that sponsors submit consent forms for FDA review; the Bureau of Drugs does not.

The two bureaus also differ in their use of the disqualification procedure. The regulations specify that a clinical investigator may be disqualified from eligibility to conduct further drug studies if he repeatedly or deliberately fails to comply with provisions of the regulations. While the Bureau of Drugs reserves disqualification for severe violations, the Bureau of Biologics has used disqualification most often as a means of forcing clinical investigators to submit overdue progress reports or other data. Upon submission of the required information, the Bureau of Biologics reinstates the investigator.

CONCLUSIONS

The Bureau of Drugs' and Bureau of Biologics' monitoring and control of clinical investigations have not been adequately coordinated. Since the same laws and regulations apply to INDs regulated by both bureaus--and often the same sponsors and investigators are involved--coordination is important. As a minimum, results of all inspections and actions taken with regard to sponsors, IRCs, and investigators should be exchanged routinely; inspection coverage should be coordinated; and sponsors, IRCs, and investigators should be treated uniformly with regard to written and oral consent and the circumstances justifying disqualification. A focal point should be established to insure the bureaus' efforts are adequately coordinated.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to establish a focal point to insure coordination of

the clinical investigation inspection and regulatory activities of the Bureau of Drugs and the Bureau of Biologics.

AGENCY COMMENTS

HEW stated that it recognizes the need for close coordination between the clinical investigation activities of the Bureau of Drugs and the Bureau of Biologics. HEW explained that the clinical investigation activities of the two bureaus also must be fully responsive to the needs, priorities, and requirements of their respective IND review processes and that therefore differences in operating procedures are sometimes appropriate.

HEW said, however, in the day-to-day operation of the clinical investigation activities of the two bureaus, exchange of information about matters of mutual concern is obviously needed. Although HEW does not see a need for a formal focal point, it said the two bureaus will identify the sponsors, IRCs, and investigators of mutual interest and exchange relevant information. Furthermore, the two bureaus will coordinate in developing new regulations and inspection programs.

CHAPTER 7

SCOPE OF REVIEW

We evaluated FDA activities and plans for regulating the testing of new drugs in humans and reviewed agency policies and procedures, legislation, and regulations. We also interviewed agency personnel.

Our review was made at FDA headquarters in Rockville, Maryland, and FDA's Bureau of Biologics and Bureau of Drugs in Bethesda and Rockville, Maryland. We also visited the Department of the Army in Washington, D.C., and NIH in Bethesda.

We reviewed the results of FDA's inspections of sponsors, clinical investigators, and institutional review committees. To give us information on a segment of the universe not previously inspected, FDA inspected, at our request, 23 sponsor/investigators and 25 clinical investigators who were testing new biological products and 35 sponsor/investigators who were testing new drug products. We also reviewed FDA's efforts to enforce compliance with the clinical investigation requirements of the FD&C Act and regulations.

FDA'S EVALUATION OF ADEQUACY OF CONSENT OBTAINED BY COMMERCIAL CLINICAL INVESTIGATORS REGULATED BY BUREAU OF DRUGS

Category	Clinical investigators
Number inspected where information on consent was obtained	153
Rated "satisfactory" (when oral consent was obtained, it was properly recorded in patient records)	99
Rated "improvement needed" (included incomplete records of written consent or defective written consent form such as use of exculpatory language)	47
Rated "unsatisfactory" (there was no notation in patient records to substantiate oral consent)	4
Rated "violative" (patient consent was not obtained from some or all test subjects)	3
	54
Failure rate (percent that did not obtain consent, document that oral consent was obtained, or use a written consent form that had all elements of consent specified)	35

FDA'S EVALUATION OF ADEQUACY OF CONSENT FORMS USED BY SPONSOR/INVESTIGATORS REGULATED BY BUREAU OF DRUGS

Category	Sponsor/investigator
Number inspected where information on consent forms was obtained	34
Rated "exemplary" (all six elements present as set forth in HEW guidelines)	13
Rated "probably adequate" (forms which depend primarily on oral presentation)	6
	a/19
Rated "need for improvement" (one or more elements missing)	8
Rated "unacceptable" (consent form included exculpatory language or failed to give balanced presentation of possible adverse effects and benefits)	7
	15
Failure rate (percent that did not have all essential elements of consent and/or contained exculpatory language)	44

a/Not adjusted for the misclassifications found by GAO and discussed on pp. 32 and 33.

FDA'S EVALUATION OF ADEQUACY OF CONSENT FORMS USED BY CLINICAL INVESTIGATORS REGULATED BY BUREAU OF BIOLOGICS (note a)

Category	Total	Clinical investigators	Sponsor/ investigators
Number inspected where information on consent was obtained	37	19	18
Rated "exemplary" (all elements present)	5	0	5
Rated "adequate" (one of four essential elements missing)	6	3	3
Rated "improvement needed" (two or more of essential elements missing)	12	4	8
Rated "unacceptable" (contained exculpatory language)	6	6	0
Deficient in recommended elements (not included in "failure rates" below)	8	6	2
	32	19	13
Failure rate (percent that did not have all essential elements of consent and/or contained exculpatory language)	65	68	61

a/The Bureau of Biologics used as its criteria for rating consent forms the four essential elements of consent explicitly required by 21 C.F.R. 310.102(h).

APPENDIX IV

MEMORANDUM OF UNDERSTANDING BETWEEN THE FOOD AND DRUG ADMINISTRATION AND THE DEPARTMENT OF DEFENSE CONCERNING INVESTIGATIONAL USE OF DRUGS BY THE DEPARTMENT OF DEFENSE

The Department of Defense (hereinafter called DOD) and the Food and Drug Administration of the Department of Health, Education, and Welfare (hereinafter called FDA) hereby jointly agree to the terms and conditions as described herein.

Purpose: To establish the procedures to be followed by the Department of Defense and the Food and Drug Administration regarding the investigational use of drugs by the Department of Defense. This Memorandum of Understanding, when signed by representatives of the agencies, replaces the current Memorandum of Understanding signed in 1964.

Background

Section 505(a) of the Federal Food, Drug, and Cosmetic Act, as amended by Section 104 of P.L. 87-781, 76 Stat. 784; 21 U.S.C. § 355(a) (1970) established procedures for the approval required before a new drug can be introduced into interstate commerce. Section 505(i) of the Act (21 U.S.C. 355(i)) establishes exemptions from the approval procedures for drugs which will be used only for manufacture of other drugs or for investigational purposes. That section provides the authority for the regulations to give effect to the general guidance of the statute, promulgated in 21 CFR 312 (formerly 130.3) by Secretary of Health, Education, and Welfare. These regulations establish the procedure and prescribe the necessary forms to be filed in order to exempt drugs to be used only for investigational purposes from the approval procedures of the Food, Drug, and Cosmetic Act.

A Memorandum of Understanding was executed by the Departments of Defense and Health, Education, and Welfare in 1964 to state the procedures that will be followed to ensure that the requirements of the Federal Food, Drug, and Cosmetic Act and the investigational drug regulations issued under that Act are fully met without jeopardizing or impeding the requirements of national security or the requirements of Federal laws and regulations relating to such use of drugs.

The Surgeon General of each Military Department has established within his office a formal "Review Board" which carefully considers each research proposal from its own agency or from outside contractors or grantees which involve the use of human subjects in the clinical

APPENDIX IV

investigation of new drugs. Each "Review Board" is staffed with highly qualified professionals capable of performing competent review of such research proposals to ensure adequate protection of human subjects. The DOD assumes full responsibility for the protection of all human subjects involved in research under its sponsorship whether this involves investigational drugs or other hazards. Before a clinical test may be performed with an investigational drug, the plan of the test and other pertinent details must be submitted to the appropriate "Review Board," the Board must indicate its approval, and the approval must be confirmed by the appropriate Surgeon General.

Experience in operating under this Memorandum of Understanding from 1964 to 1974 indicates that the DOD adheres to the standards of the FDA; that human subjects have been adequately protected in the DOD-sponsored studies; that the DOD has been able to effectively carry out its responsibilities for national security without compromise of the intent of the above-cited statutes and regulations; and that certain exemptions provided the DOD from meeting the ordinary requirements of the Investigational New Drug Regulations are no longer necessary. Accordingly, the DOD and the FDA agree to the following new procedures to meet the requirements of the Food, Drug, and Cosmetic Act concerning investigational use of drugs.

I. Substance of Agreement

The Food and Drug Administration and the Department of Defense agree that:

1. Clinical investigations that are classified for reasons of national security will not require the filing of a formal "Claim for Exemption" to the FDA. The DOD shall be solely responsible for determining the security classification of such research projects. Approval by the appropriate "Review Board" and Surgeon General of a test classified for reasons of national security will automatically exempt the drug being employed from the application of the new drug section of the Food, Drug, and Cosmetic Act during such investigational study. The DOD will report to the FDA unclassified findings associated with such studies which the FDA should be aware of in order to make a sound evaluation of non-classified studies proposed on the same or similar drugs. Additionally, the DOD will discuss its classified investigations of drugs on a frequent basis with personnel from the FDA who have proper security clearance.

2. When the unique requirements of the military dictate the extensive use in military personnel of drugs which, though not yet approved, have been tested under the Investigational New Drug Regulations

sufficiently to establish with reasonable certainty their safety and efficacy, special ad hoc review and approval for such use will be effected expeditiously through joint action by representatives of the Department of Defense and the Food and Drug Administration to ensure timely response to the military need. The DOD will report to the FDA findings associated with such use which the FDA should be aware of in order to make a sound evaluation of other studies proposed on the same or similar drug.

3. In all other cases involving the clinical testing of investigational drugs under programs sponsored by the DOD and conducted either by the DOD within its own research facilities, or for the DOD by a contractor or grantee, the ordinary provisions of 21 CFR 312 (formerly 130.3) of the Code of Federal Regulations governing the investigational use of new drugs in human beings shall be followed.

II. Name and Address of Participating Agencies

A. Department of Defense
Washington, D.C. 20314

B. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

III. Liaison Officers

A. Col. Edward J. Huycke
Director, Professional Services
Office of the Assistant Secretary of Defense
(Health and Environment)
Washington, D.C. 20301
Telephone: (202) 697-9658

B. John Jennings, M.D.
Associate Commissioner for Medical Affairs, HFM-1
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852
Telephone: (301) 443-4124

IV. Period of Agreement

This agreement, when accepted by both parties, covers an indefinite period of time and is subject to modification by mutual consent by both parties.

APPENDIX IV

V. Authority

This agreement is entered into under the authority of the Economy Act, approved June 30, 1932, as amended, 31 USC 686.

APPROVED AND ACCEPTED FOR THE DEPARTMENT OF DEFENSE

By _____

Title Acting Assistant Secretary Health and Environment

Date 24 October 1974

APPROVED AND ACCEPTED FOR THE FOOD AND DRUG ADMINISTRATION

By _____

Title Commissioner

Date 8.19.74

APPENDIX V

ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, D. C. 20301

HEALTH AND
ENVIRONMENT

April, 15, 1976

Mr. Gregory J. Ahart
Director, Manpower and Welfare
Division
General Accounting Office
Washington, D. C. 20548

Dear Mr. Ahart:

On behalf of the Secretary of Defense, we have considered the findings, conclusions and recommendations contained in the GAO Draft Report, dated January 12, 1976, "Federal Control of New Drug Testing Is Not Adequately Protecting Human Test Subjects and the General Public," (OSD Case #4262). The Department of Defense concurs in the GAO conclusions and recommendations pertaining directly to the department and contained in Chapter 5 of the report. The Department of the Army has provided some clarifying comments on this chapter which are attached.

Sincerely,

Vernon McKenzie
Acting Assistant Secretary of Defense

Enclosure

GAO note: The enclosure is omitted, but the comments contained in it have been considered in preparing the final report.

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

April 14, 1976

Mr. Gregory J. Ahart
Director, Manpower and
Welfare Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Federal Control of New Drug Testing is not Adequately Protecting Human Test Subjects and the General Public." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

John D. Young
Assistant Secretary, Comptroller

Enclosure

DEPARTMENT COMMENTS TO GAO DRAFT REPORT ENTITLED, "FEDERAL CONTROL OF NEW DRUG TESTING IS NOT ADEQUATELY PROTECTING HUMAN TEST SUBJECTS AND THE GENERAL PUBLIC"

GENERAL COMMENTS:

Questions concerning the use of human subjects in the investigation of drugs are complex and they have been the subject of continuing public controversy. For this reason, the Department welcomes any study which contributes to a better public understanding of the issues involved. Much of the material in the draft report was discussed extensively at the joint hearing by the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, and the Subcommittee on Administrative Practice and Procedure of the Senate Committee on the Judiciary. The Commissioner of Food and Drugs presented his analysis and conclusions of the inspection results in July, 1975; and in January 1976, representatives of the General Accounting Office reported the findings in this report regarding FDA's inspections of clinical investigations. Since these positions are a matter of record, our comments at this point are directed primarily at the manner in which the report analyzes the issues and the appropriateness of the proposed recommendations. Generally, we believe the report would benefit from a more extensive discussion of the underlying issues and a more thorough consideration of the way in which the proposed recommendations are likely to remedy the problems characterized in the report. This would not only improve the informative value of the report, but we believe it might alter the conclusions with respect to priorities and overall strategy.

The report bases its conclusions and recommendations principally on the GAO's interpretation of results of FDA inspections of clinical investigators. The underlying legal, medical, ethical and social issues related to protection of human research subjects, however, deserve a thorough consideration before recommendations for change are proposed. Failure to discuss such issues has obscured very real and complex problems in this area, as well as the evolving nature of the factors involved. In fact, societal standards and expectations regarding the adequacy of subject protection have undergone considerable growth since the 1962 Drug Amendments. As the Commissioner of Food and Drugs explained in his testimony, FDA has repeatedly revised its regulations as the need for additional controls has been recognized and the agency anticipates continued changes in the future. This evolutionary process means, however, that any examination which applies current wisdom retroactively, without considering the dynamics of the process, may propose changes which are already inadequate for future needs.

APPENDIX VI

Many issues involving protection of subjects and quality assurance of scientific data have been examined in a variety of studies and forums in recent years. For example, in 1972 the National Academy of Sciences/ National Research Council studied the issues involved in the monitoring of clinical investigations. This study explored a number of issues of direct relevance to this report including the responsibilities of the sponsors for the conduct of clinical trials, the extent to which sponsors should monitor on-going institutional reviews of drugs, and the FDA role in monitoring of clinical investigators. In addition, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established by an act of Congress to study matters such as patient consent to participation in research, institutional review procedures, guidelines for selection of human subjects, and a study of the ethical, social and legal implications of advances in biomedical research. In February 1975, the National Academy of Sciences conducted a public forum on "Experiments and Research with Humans: Values in Conflict." We believe the GAO report should either discuss the independent studies of issues related to patient protection such as those mentioned above, or include its own assessment of the factors which these groups considered. An adequate treatment of these issues will substantially enhance the depth and perspective of the report and probably improve the quality of the recommendations.

In evaluating the safety and effectiveness of new drugs, the Food and Drug Administration must carry out a number of complex, and sometimes competing, responsibilities. The Agency must ensure that preclinical data are sufficient to warrant testing in humans, that all data are reliable, that important new drugs are made available as quickly as possible but not before safety and effectiveness are clearly established, that design of clinical trials are adequate to justify exposure of human subjects, and that the risk to experimental subjects is minimized. Recognizing the limited resources available for these activities, an emphasis on any one area will have an impact on the level of effort that can be directed at other aspects of the regulation on Investigational New Drugs. During the past year, for example, a considerable portion of FDA's monitoring resources have been devoted to the examination of certain animal test data where the reliability has been subject to question. The report should consider the implications of its recommendations on these related responsibilities, and the extent to which difficult trade-offs will be necessitated.

Another problem with the GAO approach is that it assumes an adversarial relationship between FDA and the research community. The goals of science and medicine and of FDA regulation are the same: ethical research, scientifically valid and useful research, research protecting and benefiting both the subjects and patients generally. Achieving these objectives requires both clear exposition of FDA policies to encourage understanding

APPENDIX VI

and compliance and judicious application of sanctions in those situations where clearly improper behavior is found. For the FDA to approach researchers as though their only incentive to comply is threat of FDA action, however, demeans the ethical and professional standards of these persons and is unjustified by the evidence. Moreover, a hostile FDA might produce a reluctance to cooperate with the Agency, or worse, a disincentive for research itself.

While the preceding perspectives would have been helpful at the outset of the draft report, their absence is most critically apparent in the development of recommendations. The vast preponderance of the report analyzes the FDA inspection results, and in general the transition from the findings into recommendations is accomplished with a minimal discussion of strategies, alternatives, policy analysis, management or resource considerations. The central purpose of our comments is not to take issue with the findings, but to examine whether the proposed remedies offer constructive and effective solutions to present conditions.

There is no apparent long-term strategy underlying the GAO recommendations. The report claims its recommendations will enable FDA to improve its monitoring efforts, to achieve better regulatory control over clinical investigators, and, if supported by aggressive FDA enforcement, to compel compliance with FDA regulations through the deterrent force of legal sanctions. We cannot share this enthusiasm. Existing resources allow FDA to inspect only one investigator in a hundred each year. Thus, the vast majority of clinical investigators will be unaffected by the GAO recommendations for many years. The GAO recommendations might actually aggravate present conditions. An increase in FDA monitoring activity could signal sponsors that FDA is replacing them in the direct supervision of investigators, and thus reduce sponsor monitoring activities. FDA believes that improving rather than replacing the sponsor's oversight of investigators is the key to an effective, efficient solution to the overall problem. As the Commissioner of Food and Drugs testified in July 1975,

> " * * * FDA cannot directly police this system, which involves policing physicians and other scientists throughout the conduct of their professional work, with any reasonably attainable staff.
>
> " * * * The monitoring of clinical investigators is the direct responsibility of IND sponsors, the drug manufacturers, who are responsible for the quality and accuracy of reports to FDA and for assuring that investigators are fulfilling their scientific and ethical commitments.

" * * * Through our survey activities between 1970 and the present, we have gained a far better appreciation of the important interaction between sponsor and investigator. Apart from specific actions against poor investigators, I believe the single most helpful effort we can make will be in assuring that sponsors meet their monitoring obligations. Regulations are being prepared which will define much more clearly the responsibilities of the sponsor with respect to monitoring investigations. * * * "

These proposed regulations will require the sponsor to (1) submit to FDA written procedures for monitoring investigations, (2) assure that the investigator clearly understands his obligations prior to participation, (3) conduct periodic visits to the investigator to assure that protocol is being adhered to, (4) receive written approval of the institutional review committee, where applicable, before initiation of the investigational study, and (5) maintain accurate accounting procedures and records. Collectively, these requirements will oblige the sponsor to control investigator performance in many of the same matters where the report recommends FDA directly oversee individual investigators. We believe the approach of focusing on sponsors is a superior one in several respects. It places the legal responsibility where it properly belongs, has a much more immediate effect on all investigators, and enables FDA to verify the performance of all investigators with significantly less resource investment.

Our comments on specific recommendations reflect the FDA overall strategy.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to give priority to implementing the comprehensive p an for monitoring and evaluating clinical investigations regulated by the Bureau of Drugs and the Bureau of Biologics.

DEPARTMENT COMMENT:

The plan to which this recommendation refers was prepared in June 1974, and although its general concepts are still valid, the implementation plan for most of the specific steps is no longer accurate. In 1975, questions about the reliability of preclinical data caused substantial redeployment of inspectional resources. Preparation of many of the documents has also been affected by subsequent events. Current plans for the clinical investigation evaluation program reflect these events and remain among FDA's highest priorities.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to make better use of enforcement actions, especially the regulatory letter, to assure corrective action is taken when violations are found.

DEPARTMENT COMMENT:

[See GAO note, p. 83.]

Generally, FDA believes it is making appropriate use of available enforcement actions in instances where violations are significant enough to warrant action and as our general comments indicated, we do not believe that changes in the criteria for the use of present enforcement actions are likely to have a widespread or significant impact on the performance of clinical investigators. FDA's forthcoming regulations regarding specific sponsor responsibilities will have a more significant impact on reducing the likelihood of violations by individual clinical investigators.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to revise the regulations to provide FDA greater discretionary use of disqualification actions when regulations are violated.

DEPARTMENT COMMENT:

As noted in the comment to the preceding recommendation, FDA believes it is making appropriate use of present enforcement mechanisms. The Agency intends to revise the regulations regarding disqualification of investigators to improve the process by eliminating unnecessary procedures, by clarifying the criteria actually used by the Agency, by establishing uniform handling of actions among Bureaus, and by resolving certain legal problems that have been uncovered in practice. But these changes will in all probability not produce a sharp increase in the number of investigators being disqualified. Clarification of the obligations of investigators, together with new regulations regarding the sponsor's responsibility to monitor studies, should substantially raise the level of compliance observed by the FDA.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to:

--revise FDA regulations to conform to the elements of consent contained in the HEW guidelines.

--clearly require that written consent be obtained as a rule in Phase III trials of clinical investigations. Exceptions allowing oral consent in Phase III trials should only be permitted after obtaining FDA approval.

--require the submission of consent forms for FDA review and approval prior to initiating the clinical investigation.

DEPARTMENT COMMENT:

These recommendations focus on narrow aspects of the process of negotiating informed consent with a research subject. The concept itself has been evolving at great speed. Prior to the Drug Amendment of 1962, no statutes or regulations existed regarding consent of subjects in research. Section 505 (i) of the Act established a novel requirement with little guidance as to what was intended; since then FDA has issued its own interpretations of how consent is to be obtained, based in part on its own experience and in part on the advice of other experts. For example, the Declaration of Helsinki (1964) contains an international statement on what elements of information are essential to the process of negotiating subject consent. The HEW regulations of 1974 differed from FDA's most recent regulation (1967) in several respects: elements of consent; documentation of consent; prior approval of consent forms. Not all of these differences reflect simple policy decisions; the FD&C Act precludes mandatory submission of reports by investigators to FDA; consent is not required in every situation; the cost of compliance with requirements is not necessarily paid out of HEW grant or contract funds. Nor is the merit of some of the different requirements established; for example, prior approval of consent forms may not be as cost-effective as clearly defined requirements for such forms. The HEW regulations do not, therefore, represent definitive rules applicable to all situations, nor has any such code been yet devised. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research is currently studying subject consent, particularly as it relates to persons in unique groups such as prisoners, the mentally disabled and children. The Commission is due to make recommendations to the Secretary of HEW early in 1977.

In the evolution of public awareness and concern for the protection of human subjects, FDA continues to review and upgrade its regulations in an attempt to provide guidance in the negotiation of informed consent. The

Agency does not assume that mechanical requirements will guarantee informed consent, but believes that meaningful standards can contribute toward that goal. The FDA will propose new regulations dealing with the elements of information essential for obtaining consent, whether oral consent is ever acceptable and, if so, under what circumstances, and what consent forms must, and must not, contain. These regulations will consider the National Commission's evaluation of current HEW and FDA regulations, its recommendations for change, the need for consistency in all Departmental policies, FDA's legislative authority, and the cost-effectiveness of administrative review of documents and procedures to be utilized in individual studies to obtain informed consent.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to require sponsors to furnish information on the IRC composition and location and submit a signed statement from the IRC indicating its awareness and willingness to fulfill its responsibility as an IRC.

DEPARTMENT COMMENT:

The new regulations discussed in the general comments will require the sponsor to assure that investigators submit proposed protocols to the IRC and that the IRC has approved the protocols. The sponsor will also be required to assure that committee composition is in accordance with established guidelines and that the committee will be responsible for continuing review and approval of the investigational new drug study. The forms for reporting this information have been revised and will be in use shortly.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to develop and maintain a listing of IRC's, their location and their compostion.

DEPARTMENT COMMENT:

As indicated in the comments on the previous recommendation, FDA will be routinely receiving information on the IRC composition. Compilation of the information into a centralized listing, however, would not be significantly useful to the Agency given the current level of monitoring resources. The information that is received on IRC's will become a permanent part of the IND files, and therefore will be readily available for use in planning, directing, and conducting inspections of IRC's.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to emphasize to FDA bureaus the importance of the requirement for periodically inspecting IRC's.

DEPARTMENT COMMENT:

A periodic inspection program for IRC's cannot be created by simply emphasizing the need for these inspections. The underlying problem is one of limited resources in the face of competing priorities. While FDA plans to inspect a limited number of IRC's to the extent that current resources permit, additional inspections of IRC's would be conducted at the expense of clinical investigator and sponsor inspections. This tradeoff must be carefully considered in light of anticipated benefits.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner of Food and Drugs to include the clinical investigations sponsored by DOD in FDA's comprehensive plan for monitoring and evaluating clinical investigations, pursuant to the 1970 MOU with DOD.

DEPARTMENT COMMENT:

In many respects, this recommendation poses the same dilemma as the preceding one. Inspections of DOD sponsored clinical investigations can only be accomplished at the expense of other monitoring activities. Given the limited inspectional resources available to this program, the essential question is whether DOD sponsored investigations warrant the same, greater, or lesser coverage than other clinical investigations. Since they comprise such a small number of the total IND's, a significant coverage of this group would require a substantially disproportionate commitment of resources. According to GAO's own statistics, there were only 53 DOD sponsored investigations among the total of about 4,600 active IND's. Since FDA can only examine about 1 percent a year, a proportional commitment to DOD sponsored investigations would call for just one inspection per year. We do not believe that this is the intent of this recommendation. Instead, it implies a more extensive coverage for this group, but the report does not provide sufficient justification for concentrating on this group at the expense of coverage of other investigators. FDA will devote some coverage to DOD sponsored investigations in the future, although the level of coverage will be influenced by overall program considerations.

GAO RECOMMENDATION:

That the Secretary, HEW, direct the Commissioner, FDA, to establish a focal point to assure coordination of the clinical investigation inspection and regulatory activities of the Bureau of Drugs and the Bureau of Biologics.

DEPARTMENT COMMENT:

The Department recognizes the need for close coordination between the clinical investigation activities of the Bureau of Drugs and the Bureau of Biologics. With regard to overall policy and management considerations, the Agency presently has various mechanisms to coordinate the activities of the bureaus. In their respective areas of responsibility, the General Counsel, the Associate Commissioner for Compliance, the Associate Commissioner for Medical Affairs, as well as others, have oversight roles in assuring that FDA policies are properly implemented. As the general comments noted, the clinical investigation activities of the two bureaus also must be fully responsive to the needs, priorities and requirements of their respective IND review processes, and therefore differences in operating procedures are sometimes appropriate.

In the day to day operation of the clinical investigation activities of the two bureaus, there is an obvious need for the exchange of information about matters of mutual concern. Although GAO concludes that all inspections and actions taken with regard to sponsors, IRC's and investigators should be exchanged routinely, we do not believe the degree of congruence is sufficient to justify a total exchange of data. Instead, the two bureaus will identify the sponsors, IRC's and investigators of mutual interest and exchange relevant information. Furthermore, the two bureaus will coordinate in developing new regulations and inspection programs. We believe these steps obviate a formal focal point.

GAO note: Deleted comments pertain to material contained in the draft report but not included in the final report.

PRINCIPAL HEW AND DOD OFFICIALS

RESPONSIBLE FOR ADMINISTERING ACTIVITIES

DISCUSSED IN THIS REPORT

	Tenure of office	
	From	To
SECRETARY OF HEALTH, EDUCATION, AND WELFARE:		
David Mathews	Aug. 1975	Present
Caspar W. Weinberger	Feb. 1973	Aug. 1975
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 FOR HEALTH (note a):		
Theodore Cooper (note b)	Feb. 1975	Present
Charles C. Edwards	Mar. 1973	Jan. 1975
Richard L. Seggel (acting)	Dec. 1972	Mar. 1973
Merlin K. Duval, Jr.	July 1971	Dec. 1972
Roger O. Egeberg	July 1969	July 1971
Philip R. Lee	Nov. 1965	Feb. 1969
COMMISSIONER, FOOD AND DRUG ADMINISTRATION:		
Alexander M. Schmidt	July 1973	Present
Sherwin Gardner (acting)	Mar. 1973	July 1973
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
DIRECTOR, NATIONAL INSTITUTES OF HEALTH:		
Donald S. Fredrickson	July 1975	Present
R. W. Lamont-Havers (acting)	Feb. 1975	July 1975
Robert S. Stone	May 1973	Jan. 1975
John F. Sherman (acting)	Jan. 1973	May 1973
SECRETARY OF DEFENSE:		
Donald H. Rumsfeld	Nov. 1975	Present
James R. Schlesinger	July 1973	Nov. 1975
William P. Clements (acting)	June 1973	July 1973

	Tenure of office From	To
SECRETARY OF DEFENSE (continued):		
Elliot L. Richardson	Jan. 1973	May 1973
Melvin R. Laird	Jan. 1969	Jan. 1973
Clark M. Clifford	Mar. 1968	Jan. 1969
Robert F. McNamera	Jan. 1961	Feb. 1968
SECRETARY OF THE ARMY:		
Martin R. Hoffmann	Aug. 1975	Present
Norman R. Augustine (acting)	July 1975	Aug. 1975
Howard H. Callaway	May 1973	July 1975
Robert F. Froehlke	July 1971	May 1973
Stanley R. Resor	July 1965	June 1971
Stephen Ailes	Jan. 1964	July 1965
SURGEON GENERAL OF THE ARMY:		
Lt. Gen. R. R. Taylor	Oct. 1973	Present
Lt. Gen. H. B. Jennings, Jr.	Oct. 1969	Sept. 1973
Lt. Gen. Leon D. Heaton	June 1959	Oct. 1969

a/Until December 1972 the title of this position was Assistant Secretary (Health and Scientific Affairs). Before March 1968, the Commissioner, Food and Drug Administration, reported directly to the Secretary of Health, Education, and Welfare. Therefore, prior incumbents of this office are not listed.

b/Acting Assistant Secretary of Health from February to May 1975.

AN EQUAL OPPORTUNITY EMPLOYER

UNITED STATES
GENERAL ACCOUNTING OFFICE
WASHINGTON, D.C. 20548

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE,$300

POSTAGE AND FEES PAID
U. S. GENERAL ACCOUNTING OFFICE

SPECIAL FOURTH-CLASS RATE
BOOK