REPORT TO THE CONGRESS

Assessment Of The Food And Drug Administration's Handling Of Reports On Adverse Reactions From The Use Of Drugs B-164031(2)

Department of Health, Education, and Welfare

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

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COMPTROLLER GENERAL OF THE UNITED STATES
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To the President of the Senate and the
Speaker of the House of Representatives

This is our report on the Food and Drug Administration's handling of reports on adverse reactions from the use of drugs. The Administration is part of the Department of Health, Education, and Welfare.

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, and to the Secretary of Health, Education, and Welfare.

Elmer B. Staats

Comptroller General
of the United States

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ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act
GAO	General Accounting Office
HEW	Department of Health, Education, and Welfare
PHS	U.S. Public Health Service
VA	Veterans Administration

COMPTROLLER GENERAL'S REPORT TO THE CONGRESS

ASSESSMENT OF THE FOOD AND DRUG ADMINISTRATION'S HANDLING OF REPORTS ON ADVERSE REACTIONS FROM THE USE OF DRUGS

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D I G E S T

WHY THE REVIEW WAS MADE

GAO reviewed the Food and Drug Administration's (FDA's) system of handling reports on adverse reactions from the use of drugs to learn whether it was being used effectively to aid in drug regulation. FDA is part of the Department of Health, Education, and Welfare.

FINDINGS AND CONCLUSIONS

Each year the use of drugs adversely affects an estimated 6 million people in the United States at an estimated cost of $627 million for hospitalization, doctors' services, and loss of work.

By law, FDA is responsible for insuring that drugs involved in interstate commerce are safe and effective. Advising the public and doctors of adverse reactions caused by drugs is a fundamental part of this responsibility.

FDA obtains adverse reaction information from such sources as drug manufacturers, hospitals, doctors, and medical literature. The manufacturers submit information to both FDA's monitoring unit and regulatory divisions; the divisions are responsible for taking needed action to regulate marketed drugs.

FDA's monitoring unit is responsible for developing sources of adverse drug reaction reports and for collecting, analyzing, centrally storing, and forwarding the information to FDA's regulatory divisions. These divisions may take action on the basis of information submitted directly to them by drug manufacturers or by the monitoring unit.

Inadequate use of reporting system

FDA's adverse drug reaction reporting system has not been used adequately to regulate drugs. Some medical officers in the regulatory divisions (1) did not use it, (2) did not know it existed, or (3) were uncertain whether FDA had the burden of proving a specific drug caused an adverse reaction. (See pp. 12 and 13.)

Moreover, the regulatory divisions do not receive complete or adequate information from the monitoring unit due to deficiencies in the reporting system. (See p.15.)

GAO reviewed adverse reactions reported to the monitoring unit on 50 randomly selected drugs--a total of 1,640 reports of 620 different reactions. According to FDA medical officers, most adverse reactions were already listed in the labeling of the drugs, but 222--associated with 26 drugs--were not. Of the 222 reactions, 60, associated with 12 drugs, should probably be on the labels of these drugs, provided a causal relationship could be shown.

FDA Bureau of Drugs officials stated that, based on their further review, 24 of the 60 reactions were found to be on the labels in terminology apparently not readily recognized by the medical officers.

Drug manufacturers reported 21 of the remaining 36 reactions to both the monitoring unit and the regulatory divisions. However, the medical officers had received copies of only 1 report for the remaining 15 adverse reactions from the monitoring unit.

Bureau of Drugs officials said that these reactions might have led to labeling changes if a causal relationship had been established.

GAO interviewed 81 medical officers, 30 of whom had been with FDA from 2 to 11 years; 6 of these officers did not know that a system administered by the monitoring unit even existed, 10 were aware of the system but had never requested information, and 14 had requested information, but had never used it as the sole basis for taking regulatory actions. (See p. 12.)

GAO asked 17 of these 30 officers their opinions on FDA's responsibility for proving cause and effect relationships between marketed drugs and adverse reactions, and

--2 said they did not know who was responsible, FDA or the drug manufacturer,

--5 said the drug manufacturer must prove to FDA that its drug was safe and effective, and

--10 said FDA was responsible.

HEW's Assistant General Counsel, Food, Drugs, and Environmental Health Division, advised GAO that drug manufacturers are responsible for proving that their drugs are both safe and effective after being approved for the market. (See p. 13.)

FDA believes that its medical officers know, in a practical sense, what to do about an adverse reaction and that their efforts do not represent FDA's taking on a burden that is the manufacturer's.

According to FDA, it must be well prepared to document an association claimed to be significant if it intends to take regulatory action because the courts may have to decide whether FDA has appropriate documentation to substantiate its claims. (See p. 15.)

Need to improve the adverse drug reaction reporting system

Primary deficencies of the reporting system are that the monitoring unit

--receives only a limited number of adverse reaction reports,

--does not always obtain additional information needed to evaluate reports received,

--does not store centrally all information available within FDA, and

--does not send complete information to the regulatory divisions, nor send it on a systematic basis.

Limited reporting of adverse reactions

The reporting system has not achieved its purpose of assisting FDA in regulating drugs.

An estimated several million adverse reactions occur annually in private hospitals, but from 1960 through 1972 FDA received only a total of 75,000 reports from them.

The approximately 390 Federal hospitals could be better developed as a source of information for FDA. Federal hospitals in the United States treat about 1.8 million patients yearly; however, since 1968 these hospitals have accounted for only about 5 percent of the reports FDA has received. (See p. 19.)

FDA has two methods of obtaining information--spontaneous reporting and intensive monitoring.

Sources providing spontaneous reports include private and Federal hospitals, doctors, patients, drug manufacturers, or anyone experiencing or observing an adverse reaction.

Under intensive monitoring, specific patient populations are monitored for all adverse reactions so that such reactions can be related to drug use. From 1965 through December 1972, FDA awarded 14 contracts totaling about $5 million to 6 hospital and medical facilities for intensive monitoring. This method contributed about 2 percent of the adverse reaction reports. (See p. 26.)

Since 1971 FDA has been working toward establishing a National Center for Drug Experience Information which would include programs for intensive monitoring of drugs. (See p. 28.)

Increased adverse reaction reporting would have occurred if FDA had decided what method the monitoring unit should use to best obtain information; aggressively pursued available sources of adverse reaction reports, including Federal and private hospitals; and more effectively administered its intensive monitoring contracts.

Information not obtained to evaluate adverse reactions

Before the association between a drug and a reported adverse reaction can be properly evaluated, additional information may be required because reports may be incomplete.

In 89 adverse reaction reports the monitoring unit received, additional information had not been obtained. Such needed information is not always obtained because FDA does not have guidelines or instructions requiring it. (See p. 33.)

Adverse reaction information not centrally located

The monitoring unit was established, in part, to provide one location in FDA where adverse reaction information from all sources would be available. Having all reactions on like incidents located in one place would make it easier to identify trends. (See p. 35.)

GAO believes the monitoring unit does not serve as a central source of adverse drug reactions within FDA because the unit is not convinced of the need to centrally locate all available information. (See p. 37.)

All information not sent to the regulatory divisions

The monitoring unit does not furnish the regulatory divisions all the information it has on adverse reactions, even when the information is

specifically requested, because it considers its information sources confidential and its reporting system is not fully automated and manual accumulation of information is too time consuming. (See pp. 42 to 44.)

In summary, FDA's reporting system, to be effective, must provide complete information and provide it systematically. (See p. 47.)

RECOMMENDATION TO THE SECRETARY OF HEW

GAO recommends that the Secretary direct the Commissioner of FDA to take several actions to improve the adverse drug reaction reporting system and its use as an aid in drug regulation. (See pp. 16, 29, 37, and 47.)

AGENCY ACTIONS AND UNRESOLVED ISSUES

HEW advised that GAO's assessment of FDA's adverse drug reaction reporting system had pointed out an important FDA problem area. (See app. III.) HEW advised further that FDA has begun implementing a plan to develop a National Center for Drug Experience Information which will address a number of the major issues raised by GAO. A committee is being formed within FDA whose primary objective will be to insure that information developed by and housed in the monitoring unit will be of maximal use in drug regulation.

Specific HEW comments on GAO's recommendations and actions taken or planned to implement them are discussed in appropriate sections of this report.

MATTERS FOR CONSIDERATION BY THE CONGRESS

Information in this report should be useful to the Congress in future hearings it may hold on the overall quality of public medical care, including FDA's effectiveness in protecting the public from adverse drug reactions.

CHAPTER 1

INTRODUCTION

Drugs are one of mankind's most widely used and effective means of preventing and treating diseases and other illness. However, drugs may produce undesirable reactions which may be as serious as the sickness. There is always the risk that the use of a drug will cause the individual to have an adverse reaction, which could be as minor as a mild headache or as severe as death.

According to a Food and Drug Administration (FDA) study, each year an estimated 6 million people in the United States will suffer from adverse drug reactions. These reactions cost our society an estimated $627 million in hospitalization costs, doctors' services, and loss of productive work.

FDA is responsible, under the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended (21 U.S.C. 355), for insuring that drugs in interstate commerce are safe and effective. Advising the public and doctors of adverse drug reactions is a fundamental part of this responsibility. FDA is administered by a Commissioner under the direction of the Assistant Secretary for Health, Department of Health, Education, and Welfare (HEW).

FDA carries out its responsibilities by continuous investigation and evaluation of drugs through all stages of their development and use. Before any newly developed drug can be tested on humans, the drug manufacturer must comply with FDA regulations for testing (21 CFR 130.3). When the clinical tests demonstrate the effectiveness and safety of the drug to the satisfaction of FDA scientists, FDA may approve a "New Drug Application" permitting the manufacturer to market the drug (21 U.S.C. 355c).

Although a new drug undergoes three separate phases of clinical tests before FDA approves it for the market, the number of persons involved in these tests is necessarily limited.

--Phase I covers the first tests in humans and is generally limited to 20 to 50 persons.

--Phase II tests generally cover no more than 100 to 200 persons.

--Phase III tests may include several thousand persons.

In some instances adverse reactions to new drugs, or their frequency of occurrence, can only be discovered through widespread use of the drug rather than by clinical tests. As a result, current and cumulative data relating to adverse reactions must be continuously acquired and evaluated by FDA if it is to advise the public and doctors of unexpected hazards.

To more fully identify such hazards, FDA has undertaken study and development of new sources of information. For example, it is developing methods for monitoring national drug use trends so that classes of drugs which are of particular importance can be detected and the overall significance of regulatory actions can be assessed. In addition to collecting single reports, FDA is also supporting development of adverse reaction surveillance techniques (intensive monitoring) which can provide information on the incidence of adverse reactions to a given drug.

To serve the public safely and effectively, doctors must know the risks involved in prescribing drugs as well as the desired results expected. Only when they have all the information can doctors appropriately weigh the benefits and risks.

FDA keeps doctors informed about drugs primarily through their labeling, which includes labels attached to drug containers or wrappers and package inserts. Identical information is included in medical publications for doctors. The drug labeling lists the diseases or disorders the drug is intended to treat, situations in which it should not be used, and significant adverse reactions.

Other methods used to provide supplemental information to doctors include HEW news releases, FDA drug bulletins, revised labeling of drugs, and corrections to drug advertisements.

FDA also transmits drug information to individuals, consumer groups, and medical groups through direct communications, exhibits, speeches, and journal articles.

ADVERSE DRUG REACTION REPORTING SYSTEM

To identify information on adverse drug reactions and to assist in drug regulation, FDA created an adverse drug reaction reporting system in 1960 to alert FDA to severe reactions and to identify a trend of the same drug being associated with the same reaction. In fiscal year 1972 FDA allocated about $830,000 for operating the reporting system. In addition, since 1960 FDA has spent an estimated $6 million in contract funds to develop systems for acquiring drug experience information, including adverse reactions.

FDA obtains adverse reaction information from various sources, including drug manufacturers, hospitals, doctors, and medical literature. Drug manufacturers holding New Drug Applications are required under FDA regulations (21 CFR 130.13 and 130.13a) to report adverse reaction information to FDA. These reports, representing about 57 percent of the adverse reaction reports submitted to FDA, are received by divisions in the Office of Scientific Evaluation (referred to as the regulatory divisions), and by the Division of Epidemiology and Drug Experience (referred to as the monitoring unit). Information from hospitals and other sources is reported to the monitoring unit and other FDA organizations, such as FDA's medical library.

MONITORING UNIT

The monitoring unit administers FDA's adverse drug reaction reporting system. Essentially, the unit is responsible for developing sources of adverse reaction reports; collecting information on adverse reactions; analyzing it; centrally storing it; and, if serious reactions are involved, forwarding the information to the regulatory divisions which are responsible for taking regulatory action when necessary. The divisions may take action on information submitted directly to them by drug manufacturers or by the monitoring unit.

The monitoring unit receives adverse reaction reports in two ways--spontaneous reporting and intensive monitoring.

Under spontaneous reporting, anyone who experiences or observes an adverse reaction believed to have been caused by

a particular drug may report that experience or observation to FDA. Sources of spontaneous reports include prescribing doctors, patients, private and Federal hospitals, State health departments, pharmacists, FDA inspectors, and drug manufacturers.

Under intensive monitoring, patients assigned to a specific number of beds in selected hospitals and the drugs prescribed for them are monitored. The monitoring consists of keeping a chart on the drugs each patient receives and his reactions to them.

The monitoring unit generally receives information on adverse reactions from FDA's Drug Experience Report. As a report is received, medical officers in the monitoring unit analyze the information to determine the probability that the specific drug(s) indicated in the report caused the reaction. Their conclusions as to the cause and effect relationship are coded as follows.

--"Definite." The report established a direct cause and effect relationship between the drug and the reaction. For example, the report showed that the reaction cleared when the drug was withdrawn and recurred when the drug was readministered.

--"Probable." The report did not clearly demonstrate a direct cause and effect relationship between the drug and the reaction but the reaction was very likely caused by the suspected drug (probability greater than 50 percent).

--"Possible." The report indicated that a direct cause and effect relationship between the drug and the reaction was not likely but may have existed (probability less than 50 percent).

--"Remote." The report showed that a cause and effect relationship between the drug and the reaction was not demonstrated; was not likely; and was, in fact, most improbable although not impossible.

The monitoring unit also determines the severity of the reaction being reported. Reactions which produce no hazards to health or which would not hinder the patient in continuing

his normal life are classified as not serious. Serious reactions are those constituting a definite hazard to health which prohibit a person from following his ordinary life pattern for a significant period of time. When a report involves a serious reaction, the monitoring unit is required to forward the information to a medical officer in one of the regulatory divisions for his use in evaluating the need for possible regulatory action.

An Alert Report, prepared by the monitoring unit, was used to provide information on serious reactions to medical officers in the regulatory divisions. It included both new reactions and known reactions which had shown unexpected increases in severity or frequency or unexpected preponderances in some segment of the population, such as in children. The report was discontinued in May 1971 after 4 years of use.

Information provided by the Drug Experience Report is evaluated and coded for the computer by medical officers in the monitoring unit. This has resulted in two computer listings, one containing the adverse reactions reported to the monitoring unit from January 1966 through September 1969 and the other the reactions reported after that. The listings show the name of the drug, type of each reaction reported, and cause and effect relationship as determined by the monitoring unit.

REGULATORY DIVISIONS

Before a manufacturer is permitted to market a new drug it must submit evidence to FDA which shows the drug is safe and effective for its intended use. This burden of proof is required from the manufacturer by section 505(a) of the FD&C Act. Once FDA has approved the drug for use by the public, the manufacturer is required by section 505(e) of the act to prove the drug is safe and effective whenever new evidence indicates to the contrary.

Medical officers in the regulatory divisions are responsible for thoroughly evaluating adverse reaction information and initiating actions needed to regulate the continued marketing of drugs. Such actions may include recommending further study of the drug, issuing letters to doctors alerting them to potential dangers, requiring a change in the drug's labeling, restricting channels of distribution, or withdrawing the drug from use.

CHAPTER 2

REPORTING SYSTEM NOT FULLY USED TO REGULATE DRUGS

FDA is responsible for monitoring drugs to identify adverse reactions and, when warranted, taking regulatory action to protect the public. Although FDA's adverse drug reaction reporting system was established to assist in regulating drugs, the system has not been adequately used for its intended purpose.

In some cases FDA has not evaluated the need for regulatory action even though the reporting system contained information associating adverse reactions with particular drugs. In other cases it has not taken timely regulatory action. In our opinion, this has occurred because:

--Some medical officers in the regulatory divisions did not use the reporting system; others did not know it existed.

--Some medical officers in the regulatory divisions were uncertain whether FDA had the burden of proving a specific drug caused an adverse reaction.

--The regulatory divisions did not receive complete, accurate, or adequate information from the monitoring unit due to deficiencies in the reporting system.

FAILURE TO USE REPORTING SYSTEM

We reviewed the adverse reaction reports received by the monitoring unit from October 1969 to May 1972 on 50 randomly selected drugs. During this period about 45,000 reports on 1,441 drugs were received. Of these, 1,640 reports of 620 different reactions were on the 50 drugs. At our request medical officers in the regulatory divisions reviewed the labeling of these drugs. They advised us that, although most of the adverse reactions reported were listed in the labeling, 222--associated with 26 drugs--were not. According to them, 60 of the 222 reactions, associated with 12 drugs, should probably be on the labels of these drugs, providing a causal relationship could be shown.

We brought the 60 reactions to the attention of FDA's Bureau of Drugs, which further reviewed the matter. Bureau officials advised us that 24 of the reactions were stated in the labeling but, in most cases, in somewhat different terminology, which apparently was not readily recognized by the medical officers.

Drug manufacturers reported 21 of the remaining 36 reactions to both the monitoring unit and the regulatory divisions. However, medical officers in the regulatory divisions had received copies of only 1 report for the remaining 15 adverse reactions from the monitoring unit. Bureau of Drugs officials said that these reactions might have led to labeling changes of the drugs if causal relationships were established.

Details on 2 of the 12 drugs are as follows.

--Twelve different adverse reactions, including double vision, convulsions, and heart arrest, were reported to the monitoring unit for one drug. The medical officer responsible for regulating this drug told us in July 1972 that he had never used the reporting system maintained by the monitoring unit and did not know what kind of information the unit had or how to go about getting it.

  In November 1972 the officer said he had still not requested the reports from the monitoring unit and would not until someone explained the reporting system to him and demonstrated how it could help him.

--A second drug had nine different adverse reactions associated with it, including hallucinations, hypertension, and failure of muscular coordination.

  A medical officer told us in July 1972 that to determine if action were needed he would have to review each report. In September 1972 the officer told us he still had not contacted the monitoring unit to obtain the reports.

We met with 30 of the 81 medical officers in the regulatory divisions to obtain their comments and opinions of

FDA's adverse drug reaction reporting system. Of these, 28 were responsible for regulating the 50 drugs in our selection, and 2 were routinely contacted during the course of our audit. The 30 officers had been with FDA from 2 to 11 years.

Years with FDA	Number of medical officers
2 to 3	7
4 to 6	7
7 to 9	10
10 to 11	6
	30

Six of these officers--with 2 to 9 years of experience with FDA--did not know that a reporting system administered by the monitoring unit existed; 10--or one-third--with 2 to 11 years of experience, told us that they were aware of the system but had never requested information. Two of the 10 said they were unsure how to go about requesting information from the monitoring unit. The others said they were not too familiar with the type of information that could be obtained.

The remaining 14 officers said they had requested information but had never used it as the sole basis for taking regulatory actions, primarily because the information was incomplete and, therefore, unsuited for their purposes. (See ch. 4.)

On the other hand, we found that each veterinarian in FDA's Bureau of Veterinary Medicine receives a computer listing showing adverse reactions by animal drugs. Every 2 weeks each veterinarian receives a revised listing which is used to identify trends of adverse reactions. (See ch. 5.)

MEDICAL OFFICERS UNCERTAIN OF FDA'S BURDEN OF PROOF RESPONSIBILITY

We asked 17 of the 30 medical officers contacted during our review their opinion concerning FDA's responsibility for proving a cause and effect relationship between a marketed drug and an adverse reaction. In our opinion responsibility for proving the cause and effect relationship could affect the amount of time a medical officer spends in obtaining evidence before initiating a regulatory action.

Although the 17 officers said they would initiate regulatory action as soon as they were satisfied that an adverse reaction was associated with a marketed drug, they had varying opinions as to where the burden of proof rests.

--2 officers, who have served in their present capacities for 4 and 9 years, told us that they did not know who was responsible, FDA or the drug manufacturer.

--5, with 2 to 10 years of experience, said that the drug manufacturer must prove to FDA that its drug is safe and effective.

--10 said that FDA was responsible for proving the cause and effect relationship between a marketed drug and an adverse reaction.

One of these said that after FDA approves a New Drug Application, it no longer has authority to require the manufacturer to fully investigate adverse reactions. Another told us that FDA must build a case with conclusive evidence or at least demonstrate a strong association between the reaction and the drug before it could request the manufacturer to take any action and that if a drug has a high sales volume FDA might have difficulty getting the manufacturer to take action.

HEW's Assistant General Counsel, Food, Drugs, and Environmental Health Division, advised us that drug manufacturers are responsible for proving their drugs are both safe and effective after being approved for the market. FDA does not have to prove them unsafe or ineffective nor prove a causal relation between a marketed drug and an adverse reaction. He

said that FDA's responsibility is clearly brought out in section 505(e) of the FD&C Act (21 U.S.C. 355e) which states:

> "The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application * * * if the Secretary finds * * * that new evidence * * * not available to the Secretary until after such application was approved * * * shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved * * *."

The Assistant General Counsel said that FDA needs only to gather information indicating an association between a marketed drug and an adverse reaction, the only question being how much information is needed to show that a problem exists. He said that this must necessarily be left to the judgment of the medical officers in the regulatory divisions. We believe the following example illustrates FDA's practice in establishing such an association.

Through May 1972, FDA's monitoring unit received 73 adverse reaction reports associating a drug with temporary loss of breath and cardiac arrest. According to the reports, the drug may have been associated with 12 deaths.

In January 1971, seven medical officers met and agreed that use of the drug should be restricted and its label completely revised. Because the drug was associated with potentially fatal adverse reactions, the medical officers believed that a strong warning of the dangers was needed on the label. However, FDA spent the next 6 months--until July 1971--summarizing adverse reaction reports. During that 6-month period FDA received nine reports associating the drug with temporary loss of breath, cardiac arrest, and/or death; six reports showed the association as probable. A medical officer told us this summary was needed to conclusively establish a causal relationship between the drug and reported adverse reactions and that it was not unusual to spend 6 months preparing such reports.

FDA explained that its medical officers know, in a practical sense, what to do about an adverse reaction. If they consider it significant, they investigate the circumstances

of its occurrence, other reports of the same reaction, etc., to determine whether or not there is evidence that the reaction was associated with drug use. If such evidence is found, regulatory action might be taken. The action taken is a matter of medical, administrative, and legal judgment. FDA said that these efforts do not represent FDA's taking on a "burden" that is the manufacturer's. According to FDA, it must be well prepared to document an association claimed to be significant if it intends to take regulatory action because the courts may have to decide whether FDA has appropriate documentation to substantiate its claims.

FDA pointed out that the manufacturer is responsible for proving its drug safe and effective. On the other hand, FDA noted that the section of the FD&C Act quoted (see p. 14) provides that if the Secretary finds that new evidence not available to him until after a New Drug Application was approved shows lack of safety, the application may be withdrawn; developing and evaluating such evidence cannot be left entirely to the manufacturer. According to FDA, responsibility for burden of proof depends on what is meant by the term and, therefore, it is not surprising that the medical officers did not answer the question consistently.

DEFICIENCIES IN REPORTING SYSTEM

FDA's drug regulation has not been entirely effective, because its adverse drug reaction reporting system--intended to assist in regulating drugs--is inadequate for that purpose. Primary deficiencies of the system are:

--The monitoring unit receives only a limited number of adverse reaction reports, does not always obtain additional information needed to evaluate the reports received, and does not centrally store all information available within FDA.

--The monitoring unit does not send complete information to the regulatory divisions, nor send it on a systematic basis.

See chapters 3, 4, and 5.

CONCLUSIONS

FDA's use of its adverse drug reaction reporting system should be improved to better regulate drugs. Its drug regulation could be strengthened if the regulatory divisions made greater use of the reporting system and FDA medical officers were clearly informed of FDA's responsibility concerning burden of proof since FDA needs only to gather information indicating an association between a drug and an adverse reaction.

RECOMMENDATIONS TO THE SECRETARY OF HEW

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

--Insure that medical officers in the regulatory divisions are aware of information available in the monitoring unit and that they use it.

--Provide clarification to FDA's medical officers concerning burden of proof as it relates to establishing an association between a marketed drug and an adverse reaction.

AGENCY COMMENTS

HEW advised us that to insure that medical officers in the regulatory divisions are aware of and use information available in the monitoring unit, a two-part plan was implemented on July 1, 1973. (See app. III.)

1. A Drug Experience Information Program Liaison Group has been formed from regulatory division and monitoring unit personnel, which fosters information exchange between the two units and coordinates responses to information, such as followup efforts.

2. Meetings are held between all medical officers and consumer safety officers in the regulatory divisions and representatives of the monitoring unit to make regulatory division staff members aware of the present capabilities of the monitoring unit.

HEW said these efforts have produced results. Its comparison of a 3-month period prior to July 1, 1973, with a 3-month period immediately following implementation of the plan showed that regulatory divisions' requests for adverse reaction information from the monitoring unit increased from 29 to 43, a 50-percent increase.

HEW also advised us that clarifying the burden of proof issue could be beneficial and that FDA's Office of General Counsel will discuss this facet of the FD&C Act at a general meeting of Bureau of Drugs medical officers. Also, FDA plans to include appropriate guidance on this matter for newly appointed medical officers as part of their orientation into FDA.

CHAPTER 3

NEED TO IMPROVE COLLECTION OF ADVERSE REACTION INFORMATION

FDA's adverse drug reaction reporting system is intended to be used for gathering adverse drug reaction information, including that available from manufacturers, for FDA's use in regulating drugs. The reporting system has not achieved its purpose. We believe that increased adverse reaction reporting would have occurred had FDA decided what methods the monitoring unit should use to best obtain information, aggressively pursued these methods, and more effectively administered its intensive monitoring contracts for adverse reaction information.

LIMITED REPORTING OF ADVERSE REACTIONS

From July 1968 through June 1972, FDA's monitoring unit received 73,186 reports of adverse reactions under 2 methods--spontaneous reporting and intensive monitoring--as follows.

Method and source	Number of reports	Percent
Spontaneous reporting:		
Drug manufacturers	42,012	57
Private hospitals	23,169	32
Federal hospitals	3,306	5
Doctors, pharmacists, and patients	1,232	2
State health departments	1,121	1
FDA inspectors	632	1
Intensive monitoring	1,714	2
Total	73,186	100

About 98 percent of the reports received by the monitoring unit were sent to FDA spontaneously. Although FDA will accept reports from anyone who has experienced or observed an adverse reaction, most reports come from drug manufacturers and private hospitals.

Under the intensive monitoring method, FDA has contracted with hospital and medical facilities to develop the capability of monitoring specific inpatient and outpatient populations to determine total adverse reaction occurrences, their incidence, and their relation to drug use.[1]

Our review of literature discussing adverse reactions showed that experts agree that most adverse reactions are unreported but do not agree on the extent to which adverse reactions occur. For example, one expert estimated that adverse reactions were responsible for 5 percent of the patients being admitted to hospitals and that another 10 percent experienced an adverse reaction during their hospital stays. Other studies by experts showed that 11 to 23 percent of hospitalized patients experienced adverse reactions. Although the FDA monitoring unit may never obtain reports on all adverse reactions occurring in the United States, we believe it could obtain significantly more reports by aggressively pursuing available sources, particularly private and Federal hospitals.

Sources of information

More than 7,000 private hospitals in the United States treat 27 million patients each year. The average hospital patient receives 20 different drugs during hospitalization. If, as indicated by 1 FDA study, only 12 percent of these patients experienced an adverse reaction, FDA could receive some 3 million reports every year from private hospitals. But, from 1960 through 1972 the monitoring unit received only 75,000 reports from them. Since 1968, Federal hospitals have accounted for about 5 percent of the reports FDA has received. These hospitals provide a relatively untapped source of adverse reaction reports. About 390 Federal hospitals in the United States treat about 1.8 million patients each year. A 1970 FDA study reported that a low-cost source of spontaneous adverse reaction reports could be developed through greater use of Federal hospitals. The report noted, however, that FDA's efforts to use the hospitals have met with little success.

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[1]Contracts were also awarded to selected hospitals and payments made to cover services rendered in providing spontaneous reports.

We visited five Federal hospitals to determine why they were not submitting more reports to FDA. Although these hospitals treat about 58,000 patients annually, they reported only 129 adverse reactions to FDA during fiscal years 1970 through 1972.

Our discussions with officials of the five hospitals revealed a lack of interest in FDA's reporting program. Although hospital officials readily admit that numerous adverse reactions occur in their hospitals annually, most of their reporting programs were inactive.

For example, an official at 1 Federal hospital which treats about 20,000 patients annually told us that about 1 in 20 patients, or 5 percent, experience some type of adverse drug reaction. This would indicate that an estimated 1,000 patients experienced an adverse reaction at this hospital during fiscal year 1972. However, the hospital submitted only two reports to FDA during that year. Moreover, three of the staff doctors told us the hospital did not emphasize reporting of adverse drug reactions and the program had never been mentioned in staff meetings. The doctors stated that the program must be pushed at the hospital level before it would succeed.

Doctors of the five hospitals gave us various reasons for not reporting. Their major concerns were:

--FDA is looked upon as a regulatory agency, and some doctors said they preferred dealing with scientific agencies which take more interest in their efforts.

--Many hospitals lack the manpower and the doctors lack the time required for reporting adverse reactions to FDA.

--Several doctors didn't know how or what to report to FDA. Moreover, they said there was no emphasis by the hospitals for them to report.

--Some doctors believed reporting adverse drug reactions could result in malpractice suits.

--FDA failed to acknowledge the reports they had submitted. One doctor said some communication from FDA

would be greatly appreciated, even a post card stating that it had received his reports. Others said they had received some feedback from FDA but it wasn't meaningful for them in their day-to-day tasks. FDA explained that such responses from hospital doctors may be due to the fact that FDA generally corresponds with the hospital program coordinator and not necessarily with the doctor initiating the report.

FDA once advised doctors and hospitals of adverse reactions by means of its Report of Suspected Adverse Reactions. This report was published primarily for participants in the monitoring unit's Hospital Reporting Program which paid selected private hospitals a stipend to cover expenses of submitting spontaneous reports of adverse reactions to FDA. However, the report was also sent on request to physicians, pharmacists, drug manufacturers, medical librarians, and other interested professionals. The cases reported in the publication, summarized from the drug experience reports by the monitoring unit, showed the drug name, adverse reaction, age and sex of the patient involved, disorder for which the drug was used, and other pertinent information.

The report represented the monitoring unit's primary effort to timely communicate information to the medical community. It was first published in January 1964 and eventually reached a circulation of over 1,500 by fiscal year 1969. The report was discontinued in May 1970 because FDA felt it did not represent an appropriate, effective, and efficient means of transmitting drug experience data and was going to replace it with a more comprehensive report. The report has not been replaced. FDA explained that some of the functions of the report are accomplished through the FDA Drug Bulletin (used to disseminate information to the health profession), correct advertising, and "Dear Doctor" letters.

An Intragovernmental Procurement Advisory Council on Drugs was established in 1963 to correlate drug procurement practices and procedures among the various Federal agencies. Represented on the Council were, among others, the Office of the Deputy Assistant Secretary of Defense (Manpower-Health and Medical), Offices of the Surgeons General of the Army and Air Force, Navy Bureau of Medicine and Surgery, FDA, U.S. Public Health Service (PHS), and Veterans Administration (VA).

Under a Council agreement, all Federal hospitals were encouraged to report adverse reactions to FDA. The intention of the agreement was clearly stated in a February 1964 news release, issued by the Office of the Assistant Secretary of Defense, stating that the medical services of the Army, Navy, and Air Force, VA, PHS, and FDA had agreed on guidelines for reporting adverse reactions. In addition, technical bulletins and regulations issued by the Army, Navy, and Air Force further encouraged the reporting of adverse reactions to FDA.

We visited the Offices of the Surgeons General of the Army and Air Force and the Navy Bureau of Medicine and Surgery to determine what they were doing to report adverse reactions to FDA. All three offices told us that the hospital commanders had primary responsibility for reporting to FDA.

We believe that reporting adverse reactions to FDA by Federal hospitals was clearly the intent of the 1963 Council agreement and that FDA should aggressively attempt to have Federal hospitals fully implement this intent.

METHODS FOR OBTAINING INFORMATION

The monitoring unit (1) first used spontaneous reporting, (2) tried a combination of spontaneous reporting and intensive monitoring, (3) emphasized intensive monitoring, and (4) as of December 1972 was considering a combination of spontaneous reporting and intensive monitoring.

Spontaneous reporting

The adverse drug reaction reporting system began in 1960 with private hospitals reporting adverse reactions to FDA under contract in what FDA referred to as the Hospital Reporting Program. From 1968 spontaneous reports submitted by drug manufacturers began to be routinely sent to the monitoring unit. Since then, hospitals under the Hospital Reporting Program and drug manufacturers have provided the monitoring unit with most of its spontaneous reports.

According to FDA, some of the main advantages of spontaneous reporting are:

--The large number of patients (and thus instances of drug use) being observed permits disclosure of rare reactions.

--It is relatively inexpensive.

--It involves the medical profession and enhances its awareness of adverse reactions to drugs.

On the other hand, FDA said the method has several limitations because:

--Most doctors will not suspect a drug of causing harm to a patient unless the adverse effect has been previously described or is a type well known to be caused by drugs.

--The frequency of reporting is inversely related to the amount of detail needed, so reports are necessarily incomplete.

--The reports occur in uncontrolled situations. The number of people taking the drug is, therefore, not known so that incidence figures, which are very

important for intelligent drug use, cannot be obtained. This is especially important when the adverse reaction consists of increased incidence of a common disease. In such situations only data that provides the number of patients taking the drug as well as the number of patients who became ill can demonstrate the association.

FDA canceled the contract phase of the hospital program in 1971 because it was believed to be ineffective and so that a more comprehensive and systematic adverse reaction reporting system could be developed. From 1960 to July 1971, FDA had awarded a total of 928 contracts to as many as 199 private hospitals. The hospitals were paid an estimated $1 million under these contracts to furnish FDA with spontaneous reports of adverse reactions. After 1967 the number of hospitals with contracts gradually decreased. No contracts have been awarded since July 1, 1971.

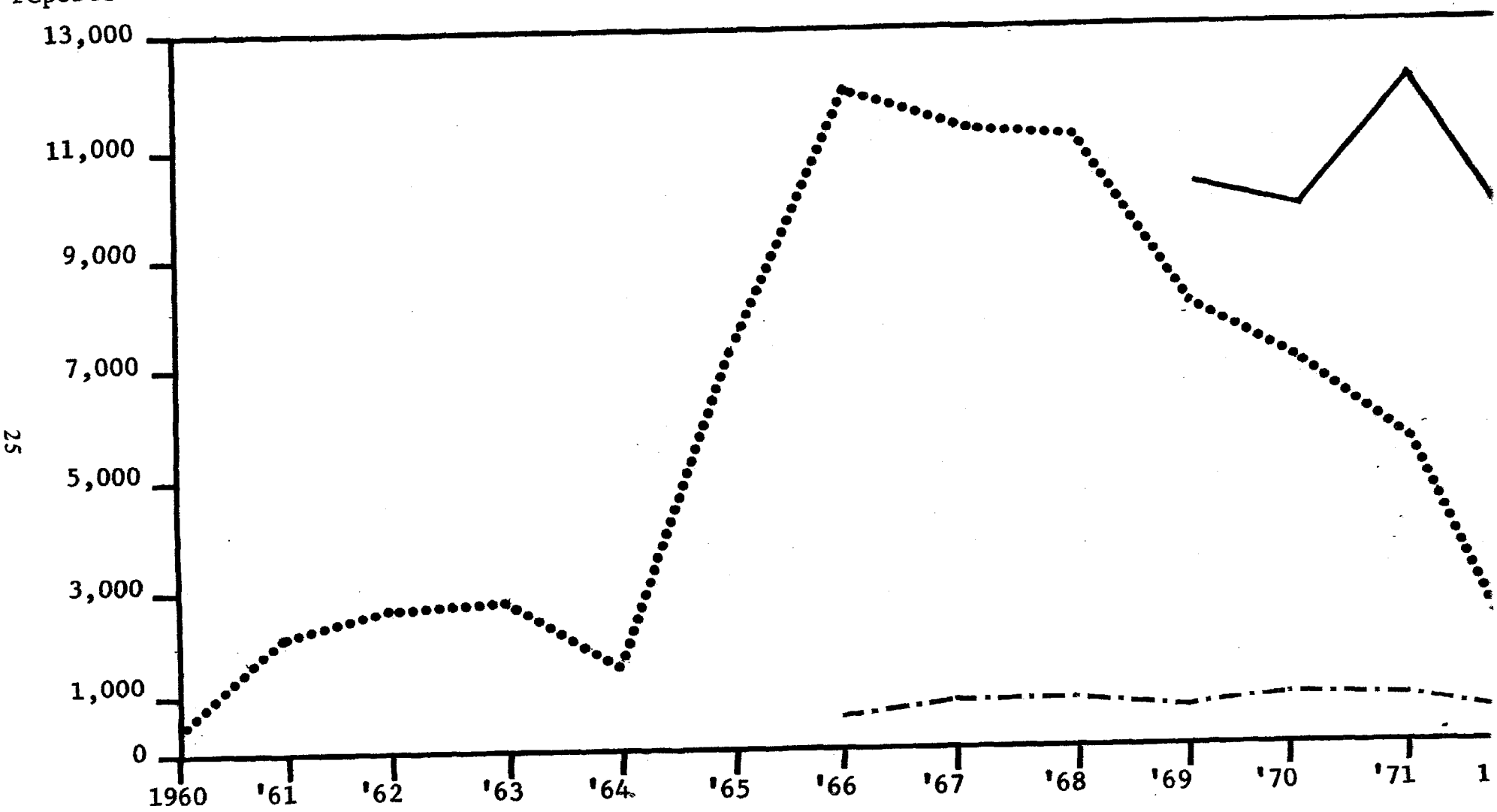
Because the hospitals were no longer paid for reporting information, the number of reports FDS received also decreased--from about 500 a month in fiscal year 1971 to less than 200 a month in fiscal year 1972. Some officials pointed out that the Hospital Reporting Program also served as a stimulus to drug manufacturers to report all reactions. We noted that, in the 8 months after the hospital program was canceled, reporting by manufacturers dropped about 25 percent. (See graph on next page.)

FDA pointed out that, under spontaneous reporting, doctors are reluctant to take the time to report relatively minor, expected, and known reactions which make up the majority of identifiable reactions.

FDA said doctors tend to regard drugs as helpful and not to consider that an adverse reaction may be due to a drug they prescribed. In general they do not report reactions that have not been previously described. Thus, FDA recognizes that it will never obtain information on all adverse reactions occurring in the United States.

FDA believes it could obtain significantly more reports by better insuring confidentiality of doctors' reports. FDA explained that it may retain as confidential, pursuant to the Freedom of Information Act (5 U.S.C. 552), names and

ADVERSE REACTION REPORTS RECEIVED BY THE MONITORING UNIT 1960 - 1972



identifying characteristics of patients, doctors, and medical institutions and, to this extent, may guarantee the confidentiality of volunteered adverse drug reaction information. FDA explained further that it may not lawfully withhold such information from congressional committees, however, and that congressional committees may lawfully release such information to the public in any form they choose; thus to this extent FDA cannot guarantee the confidentiality of such information.

Intensive monitoring

FDA decided that certain kinds of important information on adverse reactions could be obtained only through intensive monitoring. In 1970 it decided to give greater emphasis to this method of obtaining information which it believes has the primary advantages of:

--Obtaining information for controlled populations on the number of times a reaction occurred in relation to the number of times a drug was administered and other drugs taken (drug interactions). As a result, FDA can determine the rate of likelihood that an individual taking a particular drug will experience an adverse reaction.

--Recognizing when a particular event is common in the population, such as a heart attack, but is increased in frequency by a drug. Systematic intensive monitoring can detect such an increase in common events as well as identify new kinds of adverse reactions.

From 1965 through December 1972, FDA awarded 14 contracts, totaling about $5 million, to 6 hospital and medical facilities for intensive monitoring. This method has contributed about 2 percent of the adverse reaction reports.

An August 1968 FDA study concluded that the contracts awarded to that date had yielded minimal results. The study reported that none of the hospitals had provided information substantially enhancing FDA's adverse reaction program. (Since 1968, FDA has spent about $690,000 to fund additional contracts which, FDA officials state, also have provided only minimal results.)

The 1968 study further reported that one hospital had made unsatisfactory progress, primarily because FDA and the

hospital had not agreed on contract objectives, and recommended that the contract not be renewed. The project officer disagreed with the recommendation and the contract was renewed, but in June 1971 he recommended terminating this contract. He concluded that, although the hospital had successfully developed a procedure for intensive monitoring, the useful information it provided on the adverse reactions was limited. This official told us during our review that the hospital had yet to produce any information that was useful in regulating drugs. The contract was renewed through June 1973. The minutes of a Bureau of Drugs research committee meeting dated August 1971 show that the contract was renewed because it was the only ongoing study for intensive monitoring and monitoring unit officials wanted it continued.

A consultant to FDA told us in March 1972 that he believed FDA had not received any useful information from the hospital, which had been under contract since 1967 and had been paid over $600,000.

A second institution received over $4 million under two contracts awarded in May 1967 and June 1968. The contractor was working on a highly sophisticated electronic system to facilitate surveillance of drug reactions, including all medical records on some 1 million patients. The contract was terminated because of problems in obtaining mechanized reports and because information obtained was not particularly useful to FDA. One FDA official said that FDA never received any adverse reaction information. According to a January 1971 presentation by FDA on adverse drug reaction studies, the interests of FDA seemed to be secondary to those of the contractor. In its presentation FDA noted that the contractor's primary interest appeared to be using Government funds to install and maintain electronic equipment for the benefit of his medical center.

Because the contracts, according to FDA, were awarded initially to develop methodology--systems through which intensive surveillance could be accomplished--few reactions were reported. However, FDA stated that, even taking into account the relatively new and untested technology involved, it had not gained the information on reactions from its contract support it should have.

Since 1971 FDA has been working toward establishing a National Center for Drug Experience Information which would include programs for intensive monitoring of drugs. As of August 1973 FDA was in the initial development phase for such a center. A May 1971 Report of the International Conference on Adverse Reactions Reporting Systems, National Academy of Sciences--held during October 1970--estimated that the budget for such a center would be $5 million to $10 million a year.

CONCLUSIONS

FDA's adverse drug reaction reporting system has not achieved its purpose of being a means of collecting available adverse reactions.

Although it may not be practical for FDA to obtain reports on all adverse reactions occurring in the United States, FDA could obtain significantly more and better reports by aggressively pursuing available sources, including Federal and private hospitals.

We believe a major reason for the limited reporting by hospitals is FDA's failure to adequately communicate with the hospital doctors so that they know what reports are desired or whether their reports are of value to FDA. Thus, they are less likely to make any efforts to report adverse reactions.

FDA could have realized greater benefits from its intensive monitoring contracts through more effective administration.

RECOMMENDATIONS TO THE SECRETARY OF HEW

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

--Take more aggressive action to develop sources, particularly Federal hospitals, for obtaining more and better adverse reaction reports.

--Develop means of inducing these sources to report adverse reactions, including better communication with hospitals.

--More effectively administer intensive monitoring contracts to insure the desired information is obtained.

AGENCY COMMENTS

FDA has reservations about encouraging and developing the collection of large numbers of reports through spontaneous reporting because the usefulness of information from this source is a complex matter that has been of continuing concern to FDA.

HEW advised us that FDA's recent efforts to develop, distribute, and publicize its short form, "Drug Experience Report," (see p. 32) which is a source of obtaining spontaneously generated data, has been effective in inducing sources of adverse drug experience information to report to FDA. FDA received approximately 3,000 reports from private physicians during the first 10 months of calendar year 1973 as compared with an average 300 a year previously and these reports provided more significant information than FDA usually receives from spontaneous reporting mechanisms.

HEW pointed out, however, that FDA's newly formed Drug Experience Advisory Committee recently recommended that FDA abandon the collection of spontaneous reports and concentrate on intensive surveillance systems. In the Committee's view, spontaneous reporting represents a limited source of useful information. It suggested that FDA consider using a telephone reporting system to screen out inconsequential reports and facilitate reporting by all potential information sources. Other experts have advocated a mixture of spontaneous reporting and intensive surveillance.

HEW said that FDA is studying how best to obtain adverse reaction information and will review the recommendations of its advisory committee and investigate ways Federal hospitals might participate in intensive surveillance programs.

HEW told us that FDA has recently attempted to improve contract administration through better contract management training, including a 1-week course for project officers. HEW believes that the knowledge and experience FDA has gained in intensive surveillance, including better standards for measuring performance and generating precise contract requirements, has increased substantially since FDA entered into its first contracts. This should, according to HEW, insure that intensive surveillance contracts will produce better information than they did in the past.

CHAPTER 4

NEED TO FOLLOW UP AND CENTRALLY LOCATE ADVERSE REACTION INFORMATION

Medical officers in the monitoring unit analyze adverse reaction information obtained through the reporting system to determine the probability of the specific drug(s) causing the reaction and to assess the severity and significance of the reaction being reported. Efficient use of spontaneous reporting requires sifting the reports for important adverse reactions and following these up vigorously while at the same time not wasting resources pursuing known reactions or those that cannot be evaluated. The monitoring unit was established to provide, among other things, one location in FDA where all adverse reaction data would be available, so that trends could better be detected and obtaining information could be simplified.

However, the monitoring unit does not (1) always obtain additional information needed to adequately evaluate the reports it receives because FDA has no guidelines or instructions requiring the monitoring unit to follow up and (2) serve as a central information source within FDA because it is not convinced of the need to centrally locate all available information.

INFORMATION NOT OBTAINED TO EVALUATE ADVERSE REACTIONS

Before information contained in adverse reaction reports is sent to the regulatory divisions, the monitoring unit evaluates it to determine if the reaction reported was definitely, probably, possibly, or remotely related to a specific drug and to assess its severity and significance. But the reports received by the monitoring unit are usually inadequate for this purpose.

Information the monitoring unit gets is submitted on either of two forms of FDA's Drug Experience Report. Because FDA designed the report to minimize the doctor's reporting time and effort and to facilitate its use with automated data processing equipment, the reports are short and provide only

a minimum of data on which to make judgments concerning the cause and effect relationships between the drugs and the reactions. One form requires limited information about the patient, the adverse drug reaction, and the suspected drug. (See app. I.)

The second form is a shorter report devised by FDA in October 1971 in an attempt to increase the number of reports from doctors by making it easier for them to report. (See app. II.) It does not require the following information requested in the longer form.

--Patient's age, sex, height, and weight.

--Outcome of the reaction, e.g. patient died, recovered, or is still under treatment.

--Substantiating laboratory studies.

--Existing or prior disorders and past drug reaction or allergic history.

--Comments on possible association of reaction to the drug(s) involved.

In addition, the shorter form indicates that information on the disorder or reason for use of the drug(s) and the sender's comments are optional and, obviously, result in less information being provided to the monitoring unit. While this may encourage the doctor to report adverse reactions, in our opinion, it increases the need for followup of incomplete reports to obtain sufficient information for adequately evaluating the significance of the reactions. FDA recognizes the need to follow up on some of the reports it receives. Its Bureau of Medicine Manual[1] states:

> "* * * most adverse reaction and injury reports require additional investigation both to clarify obscure points and to convert them into a form in which they can be used as a basis for regulatory action * * *."

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[1]The Bureau of Medicine became the Bureau of Drugs on Feb. 1, 1970.

However, FDA does not have any guidelines or instructions requiring the monitoring unit to follow up to obtain additional data on reports of adverse reactions.

The August 1968 FDA study stated that many of the serious reactions sent to the regulatory divisions by means of the Alert Report were processed by the monitoring unit without adequate information for proper evaluation. To determine whether the situation had improved in light of the August 1968 study, we reviewed 89 Drug Experience Reports received by the monitoring unit from October 1969 to May 1972. These reports were associated with 77 adverse reactions[1] from 15 drugs included in our sample of 50 drugs.

We found that 71 of the 89 reports, or about 80 percent, were incomplete in one or more categories of information appearing on the report. The monitoring unit had not followed up on any of the 89 reports, although the causal relationship for about 50 percent of the reactions was classified as probable. The following table shows the extent of incompleteness for certain categories of these reports.

Information requested on the report	Number of reports lacking information	Percent
Other drugs used	27	30
Duration of therapy	17	19
Total daily dosage	17	19
Date of reaction	16	18
Outcome of reaction	13	15
Illness treated	12	13
Patient's age and sex	11	12

While no followup action was taken on these reports, Bureau of Drugs officials explained that 41 of the 77 reactions were either stated in the labeling in somewhat different terminology or were not considered reactions associated with the drug. In many of the remaining reports, they

[1]Some adverse reactions were reported more than once.

said, information was adequate to conclude that followup would not be profitable. As an example, they noted that some patients were receiving several drugs at the time of the adverse reaction, which would make it difficult to determine the association between a single drug and the reaction. The officials believed that these reports could thus be adequately evaluated even though they were technically incomplete.

However, the officials pointed out that possibly nine of the reactions were new and the data submitted was inadequate to permit evaluation.

Medical officers in the regulatory divisions told us that information obtained by the monitoring unit is of little value because adverse reaction reports are incomplete. They said that complete information was essential to properly determine the association between a drug and a reported adverse reaction.

INFORMATION NOT CENTRALLY LOCATED

The monitoring unit does not receive all adverse reaction information available to FDA nor does it attempt to collect it.

It was established, in part, to provide one location in FDA where adverse reaction data from all sources would be available. Ten separate study groups, including experts from within and outside FDA, concluded that centrally located data was essential to any adverse drug reaction reporting system. As early as September 1965, FDA recognized that no one location existed within FDA where an accurate count of total reactions reported could be obtained.

The reporting system does not include adverse reaction information reported to FDA during Phase III (see p. 6) of premarket clinical testing of drugs nor that reported in medical literature. If FDA is to serve as a repository for all adverse reactions associated with a drug, information from these sources must be included in the system. Since isolated reports of adverse reactions may not be considered significant, having all reactions on like incidents located in one place would make it easier to identify trends.

Premarket clinical testing

Before a manufacturer is allowed to sell a drug it must prove the drug is safe and effective to the satisfaction of FDA. To do this, the manufacturer must conduct tests on humans.

Recognizing the importance of having adverse reactions identified during Phase III of the premarket clinical tests included in its reporting system, FDA began in July 1968 to require that drug manufacturers submit a Drug Experience Report on these reactions. Since adverse reaction information identified during Phase III is normally sent to the regulatory divisions rather than to the monitoring unit, FDA was to develop a procedure whereby the monitoring unit would receive a summary of the information when the drug was approved by FDA for the market. This has not been done.

The Acting Director for the monitoring unit told us that his unit had not tried to obtain this information to include in the reporting system because the system was

intended to assist in regulating marketed drugs and he did not believe it would be a good idea to include premarket information.

Adverse reactions identified during Phase III should be included in FDA's reporting system because medical officers in the regulatory divisions consider the information important in their regulation of marketed drugs. Such information could, among other things, be used to better identify reaction trends which are an important consideration in drug regulation.

Medical literature

Although the monitoring unit is obtaining information and reports developed by FDA's Medical Library, the information is not in a useful form. The library reviews more than 275 United States and foreign medical periodicals and publishes every other week a Clinical Abstract report indexing all articles on adverse reactions and the effectiveness and safety of drugs. However, all publications must be reviewed to obtain a list of articles published against any one drug. The information can be quite significant.

For example, articles in medical periodicals on adverse reactions occurring in foreign countries are used by the regulatory divisions as one basis for taking action. In 1971 several articles reported that thousands of cases associating a drug with a severe neurological disease had occurred in Japan, Sweden, and Australia. At that time only one case had been reported in the United States. In May 1972 FDA issued a warning about this drug in its FDA Drug Bulletin, partly because of the above information.

Medical officers in the regulatory divisions consider a review of medical literature very important; 15 of them told us that their primary sources of information on adverse reactions were reports from drug manufacturers and articles in medical literature. To get information from medical literature, they must request it from the Medical Library and then correlate it with their other sources of information. Some medical officers said that FDA could more effectively regulate drugs if there were one central source for all adverse reaction reports.

The Acting Director of the monitoring unit told us that he does not use the library services because the library is a separate branch of FDA, not part of the unit. However, he said the unit should consider using the library in the future.

In 1965 the Director of the Medical Library told the Director, Bureau of Drugs, that the monitoring unit should closely collaborate with the library. In 1968 several officials of the unit reported to the Director of the Bureau of Drugs that medical literature, available within the Medical Library, was an extremely important source of information. Close collaboration between the Medical Library and the monitoring unit has still not been achieved.

CONCLUSIONS

The monitoring unit has not been furnishing the regulatory divisions with complete information because FDA has no guidelines or instructions requiring the unit to follow up on incomplete reports received when this is necessary for it to properly evaluate reactions. Furthermore, the unit has not served as a central location in FDA where all adverse reaction data would be available because the unit is not convinced of the need to centrally locate all available information.

RECOMMENDATIONS TO THE SECRETARY OF HEW

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

--Require the monitoring unit to follow up on reports of adverse reactions to obtain additional information needed to properly evaluate reactions.

--Centralize within the monitoring unit all information on adverse drug reactions now located throughout FDA.

AGENCY COMMENTS

HEW concurred with our recommendations and advised us that, to insure all needed followup is sought, guidelines will be written to help monitoring unit medical officers determine when further information is needed. HEW said it

has been made clear to medical officers in the regulatory divisions that the monitoring unit will undertake followup at their request. Also, HEW said that centralizing adverse reaction information within the monitoring unit should be an eventual goal. FDA is currently investigating the feasibility of placing information from medical literature and Phase III drug testing into the monitoring unit system.

CHAPTER 5

NEED FOR SYSTEM TO PROVIDE ALL INFORMATION TO REGULATORY DIVISIONS

The adverse drug reaction reporting system has not been effective in assisting FDA drug regulation because the monitoring unit does not furnish to the regulatory divisions all the information it has on adverse reactions, even when the information is specifically requested.

Generally, only numerical information showing the different reactions reported, number of times reported, and probable association of the drug to the reaction is provided to the regulatory divisions. Medical officers in the regulatory divisions told us that numerical information alone is not adequate to properly evaluate the reaction. Also, the monitoring unit provides information to the regulatory divisions only on request. For FDA's reporting system to be effective, we believe, it must not only provide complete information but must provide it systematically.

Furthermore, the monitoring unit considers the names of reporting hospitals as confidential. This precludes the regulatory divisions from following up on their own to obtain needed additional data.

Because the system is not fully automated, the monitoring unit must manually accumulate basic adverse reaction information, such as the patient's sex, race, age, description of reaction, illness being treated, and outcome of the case. In our opinion, this manual procedure is too time consuming to allow the unit to pull together all the information and furnish it to the regulatory divisions.

ALL INFORMATION NOT SENT TO REGULATORY DIVISIONS

We reviewed the 620 different adverse reactions associated with the 50 randomly selected drugs in our sample. Some of the reactions appeared extremely serious, and we believe they should have been brought to the attention of the regulatory divisions immediately. According to medical officers in the regulatory divisions 60 of the reactions,

associated with 12 drugs, should probably be on the labels of these drugs, provided a causal relationship could be shown. However, the monitoring unit had furnished the regulatory divisions information on only 1 of the 12 drugs, and then only after information was requested.

We also reviewed, in detail, information on two other drugs referred to us by FDA officials.

Drug A

From February 1968 through September 1971, the monitoring unit received 10 reports associating a serious adverse reaction with drug A. During the same period, the regulatory divisions made four requests to the unit for adverse reaction information on drug A and were given information identifying reactions noted in only four reports. Detailed information was not furnished because the monitoring unit provides such information only when specifically requested, and in this case it had not been.

The monitoring unit furnished no information on the other six reports because the association between the drug and the reported reaction was categorized only as "possible" in four of them and because two reports were received after the fourth request was made. Until December 1972 the unit did furnish information to the regulatory divisions on reactions categorized as possible or remote.

The two adverse reaction reports the monitoring unit received after the last request for information by the regulatory divisions were not furnished to them. This was true even though the unit classified cause and effect relationship of the reactions to the drug as "probable."

Until we brought the other reports to his attention, the medical officer responsible for initiating regulatory actions on drug A was not aware that 10 cases of the adverse reaction had been reported to the monitoring unit.

The following table shows the sequence of reports the monitoring unit received and the requests for adverse reaction information on drug A made by the regulatory divisions.

Date report received	Accumulated number received	Date information requested	Number of reports furnished
Feb. 1968	1		
Apr. 1968	2		
Oct. 1968	3		
Feb. 1969	4		
Apr. 1969	5		
		Aug. 1969	2
		Oct. 1969	2
Oct. 1969	6		
Sept. 1970	7		
Mar. 1971	8		
		May 1971	2
		June 1971	4
July 1971	9		
Sept. 1971	10		

In August 1971 FDA requested the manufacturer to add a warning of this adverse reaction on the label of drug A. In June 1972 a warning was added.

Drug B

From December 1967 through November 1969, the monitoring unit received four reports associating a serious adverse reaction with drug B. However, the unit did not advise the regulatory divisions of them because the regulatory divisions, unaware of the reports, had not requested any information. Had information been requested, the unit would have provided information on only two of the reactions--those categorized as probably related to drug B.

On April 18, 1972, we brought the four reports to the attention of a medical officer in the regulatory divisions. Based on the information we provided, the medical officer reviewed his files and, in May 1972, requested the manufacturer to revise the label of drug B. In April 1973 the labeling was revised.

In December 1972 the monitoring unit changed its method of furnishing information so that all reported reactions would be sent to the regulatory divisions whether definitely, probably, possibly, or remotely associated with a drug.

However, the unit will continue providing information only when requested and then only providing numerical information on the number of reactions received. We believe the monitoring unit should further change its method to systematically provide complete information.

The monitoring unit's instructions require it to forward all information on serious reactions to the regulatory divisions for in depth evaluation and consideration of regulatory action. Until May 1971 serious reactions were provided to the regulatory divisions in an Alert Report prepared by the monitoring unit. According to the Acting Director of the monitoring unit, the report was discontinued because it put too great a burden on the monitoring unit's resources to prepare and because the regulatory divisions were not using it. Contrary to its instructions, the unit has not routinely provided information on severe reactions to the regulatory divisions since May 1971.

The Acting Director told us that the unit is now considering a new Alert Report consisting of a computer printout to be prepared each week, which would provide only numerical information on the drug and the reported reactions. Rather than merely considering a new Alert Report, we believe the monitoring unit should implement its instructions, which already require that a summary report be prepared including a description of the case and the reaction.

Names of reporting hospitals considered confidential

A medical officer in the monitoring unit told us that, even when the regulatory divisions request the basic adverse reaction reports, all available data is not sent. We found that the unit treats adverse reaction reports received from Federal and private hospitals--37 percent of the reports received--as confidential and will not furnish the names of the reporting hospitals to the regulatory divisions. FDA said this arrangement creates a single focal point for dealing with the hospitals, thus eliminating unnecessary and confusing duplication of effort. The regulatory divisions, without knowing the source, cannot obtain additional information needed in analyzing adverse reactions. In our opinion the monitoring unit should either obtain the additional information needed or provide the names of reporting hospitals to the regulatory divisions so they can follow up.

Reports from drug manufacturers represent about 57 percent of the total reports the monitoring unit receives. However, the regulatory divisions also receive these reports directly from the manufacturers and, therefore, can follow up if necessary.

NEED TO AUTOMATE REPORTING SYSTEM

The adverse drug reaction reporting system is not fully automated although FDA has been trying to develop such a system since 1964. As of January 1, 1973, FDA's computer operation provided the monitoring unit with a computer listing showing the drugs, different reactions reported, number of times a reaction had been reported, and association of the drugs to the reactions.

Because its computer operation is not fully automated, the monitoring unit must make a time-consuming manual search of its adverse reaction data. As a result the unit cannot reasonably provide all of its information to the regulatory divisions. The nature and volume of information received requires a fully automated system for FDA to be able to pull together all information regarding a particular drug.

As of December 1972 the monitoring unit had received about 147,000 reports covering an estimated 2,500 different drugs. Only 106,000 of these reports had been put in FDA's computer system and printed on two computer listings. (See p. 9.) The remaining 41,000 were reports received before 1966 and were in storage.

Before December 1972 the monitoring unit had to go through the following procedure to provide just numerical information.

--Examine both computer listings for the trade and generic name of the drug. (See picture on page 45.)

--Prepare a handwritten list of the reactions and number of times they were reported. (A medical officer told us he had recently prepared a list 34 feet long.)

--Review the list to determine the total number of times each different reaction was reported and alphabetize the reactions.

--Prepare a memorandum to transmit the information to the regulatory divisions.

PRINTOUTS OF ADVERSE REACTIONS
THE MONITORING UNIT RECEIVED
OCTOBER 1969 TO MAY 1972

Four printouts consist of (1) alphabetical listings by reactions and associated drugs, (2) the details for the listing, (3) alphabetical listing by drug and associated reaction, and (4) details for the listing.

Since December 1972 the monitoring unit has modified its computer operation, and the computer can now print a listing showing the total number of times each different reaction has been reported on a particular drug. Numerical information alone, however, is inadequate for use in regulating drugs. To get more than numerical information, such as the patient's age, race, sex, illness being treated, description of the reaction, and outcome of the case, the monitoring unit must refer to the basic adverse reaction reports.

Although 45,000 of the 106,000 reports in the computer system are also on microfilm, more than 61,000 are stored in boxes. To obtain information on microfilmed reports, the monitoring unit can use a microfilm viewer-printer, which facilitates the procedure. But to obtain the information on the other reports, the reports must be found by a manual search of the boxes. A medical officer in the unit told us that obtaining more than numerical information can take considerable time; in one instance, obtaining requested information would have taken 40 to 100 hours, so the information was not furnished.

In contrast, we found that information contained in the Bureau of Veterinary Medicine's less complex adverse drug reaction reporting system appeared to be more readily accessible. For example, its computer listing showed the drugs, adverse reaction report number, date report received, report source, number of animals affected, whether followup data was obtained, and date any regulatory action was taken. To obtain additional data, the veterinarian must make a manual search. However, all reports are filed by manufacturer's name and the drug they pertain to, permitting ready access to the basic report.

Furthermore, all adverse reaction reports concerning veterinary drugs are acknowledged. Followup information is requested as needed. A file is maintained and a second followup notice is sent if a response is not received within 30 days.

Plans for automation

Since 1964 FDA has been trying to design an automated system for monitoring adverse reactions. During this time FDA has changed computer hardware and software, staff, and concepts for automating the system.

FDA system analysts told us the main factors hampering development of a fully automated system were that FDA has not decided on the objectives of the systems, who will use the information, nor data to be produced by the system. They also said no formal plans have been developed for transferring existing information into the new system. Until these basic steps are completed, the analysts said, they cannot develop a system.

CONCLUSIONS

The reporting system provides information to the regulatory divisions only upon request, does not provide all the information, and does not provide it systematically. FDA needs to fully automate its computer system to allow the monitoring unit to furnish complete information to the regulatory divisions systematically. This is essential to an effective reporting system.

RECOMMENDATIONS TO THE SECRETARY OF HEW

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

--Require the monitoring unit to systematically furnish information to the regulatory divisions.

--Require the monitoring unit to furnish all available adverse reaction information received on a drug by FDA when requested by the regulatory divisions.

--Insure that the monitoring unit complies with its instructions to furnish reports of severe reactions to the regulatory divisions when it receives them.

--Correct problems hampering development of an automated system so that all adverse reaction reports will be readily available for FDA's use.

AGENCY COMMENTS

HEW concurred with our recommendations and advised us that:

--The monitoring unit's ability to systematically furnish information to the regulatory divisions will

depend to some extent on progress in FDA's automated data system. FDA is presently considering methods for furnishing on a regular basis important information, such as data indicating significant adverse reaction trends or periodic reviews of selected drugs or drug classes.

--FDA has implemented procedures to make all information in its computer and microfilm files available to medical officers in the regulatory divisions and has so informed the medical officers.

--All significant reports, that is, reports of serious adverse reactions which do not appear in the drug labeling or which suggest an unexpected increase in the incidence of a serious reaction, are now forwarded on a weekly basis to the regulatory divisions.

--Much progress has been made in developing an automated system since our review. The monitoring unit has computerized the information received after October 1969 and no longer must retrieve such data manually. Incorporation of data received between 1966-69 is planned.

CHAPTER 6

SCOPE OF REVIEW

We primarily reviewed the operations of FDA's adverse drug reaction reporting system administered by the monitoring unit, doing most of our work at FDA headquarters in Rockville, Maryland, from December 1971 through December 1972.

We analyzed reports and publications prepared by FDA and other experts and reviewed applicable FDA regulations, policies, and practices pertaining to the adverse drug reaction reporting system and drug regulation. We reviewed the adverse reaction reports received by the monitoring unit on 50 randomly selected drugs and 5 other drugs referred to us by FDA officials.

We interviewed FDA officials in the Bureau of Drugs, including 30 medical officers in the regulatory divisions, concerning their use of the reporting system. We talked to HEW's Assistant General Counsel for Food, Drugs, and Environmental Health about FDA's responsibility for establishing the causal relationship of marketed drugs and adverse reactions. We also interviewed officials of military, VA, and private hospitals and representatives from the Offices of the Surgeon Generals of the Army and Air Force and the Navy Bureau of Medicine and Surgery to obtain comments and opinions on the system.

In addition, we reviewed the records and talked with veterinarians in FDA's Bureau of Veterinary Medicine to learn how its system for monitoring adverse reactions was operated.

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DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

DRUG EXPERIENCE REPORT

Form Approved
Office of Management and Budget No. 57-R0004

DATE SENT TO FDA *(Mo, day, yr)* | 1. ☐ INITIAL REPORT ☐ FOLLOW UP REPORT | 2. PATIENT INITIALS AND IDENTIFICATION NUMBER | 3. ACCESSION NO. *(For FDA use only)*

SECTION I. BASIC REACTION DATA

4. SEX	5. HEIGHT / WEIGHT	6. DATE OF BIRTH	7. ORIGIN	8. DATE OF REACTION ONSET
☐ M ☐ F	ins. / lbs.	mo / day / yr	☐ CAUC ☐ NEGRO ☐ ORIENTAL ☐ AMERICAN INDIAN ☐ OTHER	mo / day / yr

9. SOURCE OF REPORT *(Mfg, Hospital, etc)(Name of reporting Physician is optional.)*

10. ADDRESS OF SOURCE *(Give Street, City, State, and Zip Code.)*

11. DESCRIBE SUSPECTED ADVERSE REACTION(s) AND ANY POSSIBLE ASSOCIATION WITH THE DRUG(s) INVOLVED

12. OUTCOME OF REACTION TO DATE
- ☐ ALIVE WITH SEQUELAE
- ☐ RECOVERED
- ☐ STILL UNDER TREATMENT
- ☐ DIED *(Give date and cause)*

13. LIST ALL THERAPY IN ORDER OF SUSPICION *(Manufacturer; List NDA or IND No.)*

NAME OF DRUGS TRADE *(Generic)*	MANUFACTURERS CONTROL NO.	DOSAGE FORM *(tab, cap, etc.)*	TOTAL DAILY DOSE	ROUTE *(po, im, iv, etc.)*	DURATION OF THERAPY	DATES OF ADMINISTRATION	14. DISORDER OR REASON FOR USE OF DRUG

SECTION II. IMPORTANT MODIFYING DATA

15. SUBSTANTIATING LABORATORY STUDIES *(Clinical Laboratory, Autopsy, X-Ray, etc.)*
CLINICAL LAB: ☐ DONE ☐ ATTACHED ☐ NOT DONE
BIOPSY/AUTOPSY: ☐ DONE ☐ ATTACHED ☐ NOT DONE

16. LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS *(Include household products, industrial and agricultural chemicals)*

17. EXISTING OR PRIOR DISORDERS AND PAST DRUG REACTION OR ALLERGIC HISTORY

PREVIOUS EXPOSURE TO SUSPECTED DRUG OR RELATED COMPOUND ☐ YES ☐ NO

18. *(a)* IF FEMALE GRAVIDITY ☐☐ PARITY ☐☐ *(b)* IF PREGNANT WEEKS OF GESTATION ☐☐

19. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ YES ☐ NO

FOR FDA USE ONLY | **FOR MFG USE ONLY**

20. REACTION FACTORS *(Check all applicable boxes)*
☐ DECOMPOSITION OF DRUG ☐ INTERACTION OF TWO OR MORE DRUGS ☐ DRUG NOT USED ACCORDING TO LABELING ☐ DRUG OUTDATED
☐ DRUG MISUSED BY PATIENT ☐ OVERDOSAGE ☐ DRUG MISLABELED ☐ CONTAMINATION OF DRUG ☐ OTHER DRUG MISUSE *(Specify)*

FD FORM 1639 (12/72) *SEE INSTRUCTIONS ON REVERSE* *Use additional sheet if necessary.*

EXAMPLE OF LONG FORM DRUG EXPERIENCE REPORT

DRUG EXPERIENCE REPORT *(IN CONFIDENCE)*			Form Approved OMB No. 57-R0071
PATIENT INITIALS *(Optional)*			DATE OF REACTION ONSET
SUSPECTED REACTION(S)			
SUSPECTED DRUG(S); TRADE/GENERIC NAME *(Manufacturer's name, if possible)*			
DISORDER OR REASON FOR USE OF DRUG(S) *(Optional)*	ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION
OTHER DRUGS TAKEN CONCOMITANTLY			
COMMENTS *(Optional)*			
PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE			

FD FORM 1639 a (6/72)

EXAMPLE OF SHORT FORM DRUG EXPERIENCE REPORT

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

DEC 13 1973

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

Dear Mr. Myers:

The Secretary has asked that I respond to your request for our comments on a draft of your report to the Congress of the United States entitled "Assessment of FDA's Adverse Drug Reaction Reporting System". Our comments are enclosed.

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

Sincerely yours,

John D. Young
Assistant Secretary, Comptroller

Enclosure

on July 1, 1973: (1) A Drug Experience Information Program (DEIP) Liaison Group has been formed from both regulatory division and monitoring unit personnel. The Liaison Group fosters information exchange between the two units and coordinates responses to information, such as follow-up efforts. (2) So that all regulatory division staff members are made aware of the present capabilities of the monitoring group, meetings have occurred or are scheduled involving all medical officers and consumer safety officers in the regulatory divisions and representatives of the monitoring unit. These efforts already have borne some fruit. Comparison of a three-month period prior to July 1, 1973 with a three-month period immediately following implementation of the plan shows that the number of search requests received from the regulatory divisions has increased from 29 to 43, a 50% increase.

GAO RECOMMENDATION

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

> Provide clarification to FDA's medical officers concerning burden of proof as it relates to establishing an association between a marketed drug and an adverse reaction.

DEPARTMENT COMMENT

Clarification of the complex issue raised by the GAO report could be beneficial. Toward this end, the Office of the General Counsel has agreed to discuss this facet of the Food, Drug and Cosmetic Act at a general meeting of Bureau of Drugs medical officers. Also, we plan to include appropriate guidance on this matter for newly appointed medical officers as part of their orientation into FDA.

As indicated in Chapter 3, however, FDA does not agree that a genuine problem area has been identified here.

GAO RECOMMENDATION

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

> Take more aggressive action to develop sources, particularly Federal Hospitals, to obtain more and better adverse reaction reports.
>
> Develop means of inducing these sources to report adverse reactions, including better communication with hospitals.

DEPARTMENT COMMENT

Recent efforts toward developing, distributing, and publicizing the "short forms" have been effective in inducing sources of adverse drug experience to report to FDA. Our analysis of results thus far indicates not only that we have received more reports from the private practitioner (approximately 3,000 reports thus far as opposed to an average of 300 per year previously) but also that these reports provide more significant information than we usually receive from spontaneous reporting mechanisms. As noted in the General Comments, in spite of this apparent improvement, FDA's newly formed Drug Experience Advisory Committee (DEAC) strongly feels that spontaneous reporting represents a limited source of useful information. They have suggested, however, that FDA consider the use of a telephone reporting system as a mechanism to screen out inconsequential reports and to facilitate reporting by all potential sources of information. We are currently reviewing this recommendation. FDA will also investigate means by which Federal hospitals might participate in intensive surveillance programs.

GAO RECOMMENDATION

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

> More effectively administer intensive monitoring of contracts to ensure that the information desired under such contracts is obtained.

DEPARTMENT COMMENT

FDA has recently attempted to improve contract administration through better contract management training, including a one-week course for project officers. In addition, the knowledge and experience in the area of intensive surveillance has increased substantially since FDA entered into its first contracts. We are thus more aware of the potential of such reporting systems and have better standards against which to measure performance and with which to generate precise contract requirements. The improved FDA contract procedures and greater knowledge and experience in the field should ensure that intensive surveillance of contracts will produce better information than they did in the past.

GAO RECOMMENDATION

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

> Follow-up on reports of adverse reactions to obtain additional information needed to properly evaluate reactions.

DEPARTMENT COMMENT

We concur with this recommendation. In order to assure that all needed follow-up is sought, guidelines will be written to help the monitoring unit medical officer determine when further information is needed. In addition, it has been made clear to medical officers in the regulatory divisions that the monitoring unit will undertake follow-up at their request.

GAO RECOMMENDATION

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

Centralize within the monitoring unit all information on adverse drug reactions now located throughout FDA.

DEPARTMENT COMMENT

We concur with this recommendation as an eventual goal. The Agency is currently investigating the feasibility of placing information from the medical literature and Phase III investigations into the monitoring unit system.

GAO RECOMMENDATION

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

Require the monitoring unit to systematically furnish information to the regulatory divisions.

DEPARTMENT COMMENT

We concur with this recommendation. Carrying it out will depend to some extent on progress in our automated data system. We are presently considering methods for furnishing on a regular basis important information, such as data indicating significant adverse reaction trends or periodic reviews of selected drugs or drug classes.

GAO RECOMMENDATION

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

Require the monitoring unit to furnish all available adverse reaction information received by FDA on a drug when requested by the regulatory division.

DEPARTMENT COMMENT

We concur with this recommendation and have implemented it. All information in the computer file as well as in the microfilm files is presently available to medical officers in the regulatory divisions and the medical officers have been informed of this.

GAO RECOMMENDATION

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

> Ensure that the monitoring unit complies with its instructions to furnish reports of severe reactions when received.

DEPARTMENT COMMENT

We concur with this recommendation. All significant reports, that is, reports of serious adverse reactions which do not appear in the drug labeling or which suggest an unexpected increase in the incidence of a serious reaction, are now forwarded on a weekly basis to the regulatory divisions.

GAO RECOMMENDATION

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

> Correct those problems hampering development of an automated system so that all adverse reaction reports will be readily available for FDA's use.

DEPARTMENT COMMENT

We concur with this recommendation. Much progress has been made since the GAO assessment of our capabilities in this area were initiated. The monitoring unit has computerized information received after October 1969, and no longer must retrieve such data manually. Incorporation of data received between 1966-1969 is planned.

COMMENTS OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ON A DRAFT REPORT OF THE GENERAL ACCOUNTING OFFICE ENTITLED, "ASSESSMENT OF FDA'S ADVERSE DRUG REACTION REPORTING SYSTEM"

GENERAL

Evaluation of adverse reactions to discover which of the estimated 6,000,000 adverse drug reactions that occur in any year are new and significant is a major FDA responsibility. The assessment of FDA's Adverse Reaction Reporting System by GAO has pointed to an important FDA problem area and offered recommendations to deal with it. The Agency has reservations about one aspect of the report, however. The report emphasizes "limited reporting of adverse reactions" as a major problem and suggests that sources of spontaneous reports should be encouraged and developed in order to collect larger numbers of reports. The usefulness of such information is a complex question that has been of continuing concern to FDA. Within the last few weeks, the FDA's Drug Experience Advisory Committee has recommended that the FDA abandon the collection of such reports and concentrate on intensive surveillance systems. Other experts have advocated a mixture of spontaneous reporting and intensive surveillance. How best to obtain adverse reaction information will remain the subject of continuing FDA deliberation.

FDA has begun implementation of a plan, first proposed in October of 1971, to develop a National Center for Drug Experience Information (NCDEI) which will address a number of the major issues raised by the GAO. In addition, a committee is now being formed within the Agency which will have as a primary objective assuring that information developed by and housed in the unit will be of maximal usefulness in drug regulation.

Our comments on GAO's recommendations follow.

GAO RECOMMENDATION

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

> Assure that medical officers in the regulatory divisions are aware of information available in the monitoring unit and that they use it.

DEPARTMENT COMMENT

We concur. To assure that all medical officers in the regulatory divisions are fully aware of, and use information available in the monitoring unit, a two-part plan was implemented

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

	Tenure of office	
	From	To
SECRETARY OF HEALTH, EDUCATION, AND WELFARE:		
Casper W. Weinberger	Feb. 1973	Present
Frank C. Carlucci (acting)	Jan. 1973	Feb. 1973
Elliot L. Richardson	June 1970	Jan. 1973
Robert H. Finch	Jan. 1969	June 1970
Wilbur H. Cohen	Mar. 1968	Jan. 1969
John W. Gardner	Aug. 1965	Mar. 1968
ASSISTANT SECRETARY FOR HEALTH:		
Charles C. Edwards	Mar. 1973	Present
Richard L. Seggel (acting)	Dec. 1972	Mar. 1973
Merline 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. Goodard	Jan. 1966	June 1968
Winton B. Rankin (acting)	Dec. 1965	Jan. 1966

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