Food and Drug Administration Drug Experience Reporting System*

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During the past decade or more, a need which has become progressively important to safety in the use of drugs has been the existence of a system for adequately monitoring side effects. This necessity was acknowledged as early as 1955 by the Food and Drug Administration when a Pilot Program for the collection of new adverse drug reactions was first established. This original reporting program subsequently grew into a permanent retrieval network, then into a comprehensive center for drug reaction data, and more recently has incorporated the capabilities of data automation.

The subject of adverse drug reactions is no doubt one of the most challenging and difficult areas for study within the fields of pharmacology and therapeutics. Yet it is possibly the most vital when attempting to assess safety in the use of drugs. Much of the difficulty surrounding the subject has arisen from the many conflicting interpretations, and even the many differences in the basic definitions of an "adverse drug reaction." It is well known, for example, that what may be considered as an undesirable side effect by one physician may be in fact the precise therapy wanted by someone working in another specialty. Comprehensive data on the subject is not readily available, nor is it the frequent practice for descriptions of adverse experiences to be voluntarily forwarded; these circumstances further limit the degree of knowledge that exists. Still, it is imperative that every clinician have access to full information regarding possible adverse effects, to be able to estimate what is now commonly described as the "benefit to risk" ratio, before prescribing any drug.

Since, however, the Food and Drug Administration is directly concerned with the question of safety in the use of therapeutic agents, it has been essential that this agency attempt to develop and maintain a current and all-inclusive knowledge of every significant and potentially significant side effect of all drugs. In reviewing this topic, the establishment of the FDA system is presented, describing its evolutionary development into the present facilities of the Drug Experience Information Center.

When the original pilot study was implemented in 1955 and the collection of adverse effects was actively begun, five hospitals were chosen to serve as the original sources of information. The objectives of this study were basically to explore the feasibility of having selected institutions, working under direct contract to the Food and Drug Administration, for the purpose of forwarding reports of adverse side effects observed in clinical practice. Pharmaceutical manufacturers at that time were not required to submit information relating to adverse experiences in their routine reports. Since the value of the pilot study became quite evident in the subsequent years, a new, formal Hospital Reporting Program for the detection of adverse drug reactions in clinical practice was established in January of 1960 and is still in effect at the present time. Since its establishment, this program has repeatedly demonstrated the value of this approach as a continuing route of reliable, well documented information.

In the course of the development of this work at the Food and Drug Administration, numerous other sources of information and approaches to the actual collection of adverse reaction data have been utilized. These have included the abstracting of patients' charts by medical record librarians, the making of arrangements within hospitals where pharmacists have served as the center for retrieving information, and various procedures which utilized the services of physicians who were either in some phase of training or actually members of the hospital staff. Experience has shown patients' charts to be a relatively limited source of adverse reaction data, due to the deficiencies in total recording of entries relating to these events. The probability of being able to obtain consistently, directly from a chart, all of the background needed for a proper evaluation, is therefore quite limited. While many hospital pharmacists have provided excellent assistance in promoting adverse drug reaction reporting programs within hospitals, and help in coordinating the actual collection of reports, it is believed unwise and unfair to assign to pharmacists the primary responsibility for making the clinical determinations of whether or not a drug reaction occurred in the patient. Therefore, while other members of the hospital staff can provide valuable assistance to the physician, it is believed that the physician's judgment is required in the detection, or at least in the confirmation, of reports. The physician has accordingly become our prime source of material. It has been found further that the optimum opportunity for

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detecting drug reactions is to be had through the periodic observation or screening of patients for such effects during a hospital admission. The ideal program has therefore incorporated procedures for the daily screening and the recording of adverse drug reactions as part of the physician's normal hospital routine. It is difficult to stress too emphatically the importance of collecting adequate data relating to cases of reactions, since the entire evaluation process which follows is completely dependent on both the quantity, and more importantly, the quality of the information that has been retrieved.

As also indicated earlier, one of the most difficult questions that has been encountered when working in the field of adverse drug effects is that of establishing an actual definition of a "drug reaction." A fine line, for example, appears to exist between what can be called an extension of the known, or anticipated, pharmacologic activity, and the beginning of an adverse effect. Overdosage from an established hypnotic agent may or may not be defined as an adverse effect, depending upon the severity of the result, the state of knowledge concerning the particular agent, the possibility of a new mechanism of synergism, or even the frequency or popularity of the event. There may be, in addition, as many interpretations of the words significant, dangerous, unusual, new, severe, untoward, undesirable, serious, or unexpected as there are physicians to make the interpretations. These differences in definition or interpretation of what might be defined either as a "side effect," "adverse effect," "adverse reaction," or "adverse experience" probably account for much of the misunderstanding about the subject and the great variations in data that have been published about drug reactions.

Consequently, it has become evident through experience that no single definition will suffice to describe a "drug reaction" in all of its connotations. In contract programs, such as those at the Bureau of Medicine, this problem is further compounded by the budgetary requirement of having to justify payments for all cases accepted, yet not applying criteria so rigid that they will restrict potentially valuable information. To attempt to clarify this question more precisely for those who are routinely reporting under such contracts, another term, "reportable reaction" has been used. For practical purposes, this term may preclude the semantic differences in definitions and allow a physician the latitude of being able to forward any case which he personally feels to be significant, or of probable interest. The interests of the Bureau of Medicine in implementing this work are, of course, to attempt to detect reports of potentially significant, unprecedented reactions, involving the newer therapeutic agents. It has been learned through experience, however, that the requirements for reporting cases should not restrict this coverage only to those drugs that can be chronologically defined as "new." In the past several years for example, certain reactions of marked significance were first noted in one category of drugs that had been commonly used in clinical practice for approximately 15 years. Furthermore, even the most well established therapeutic agents can contribute to adverse reactions with other drugs, through actions of either synergism or antagonism. While the FDA objectives at the current time are therefore directed primarily toward insuring the necessary monitoring of the newer agents, surveillance of all drugs is attempted through the programs which are now in effect.

The Food and Drug Administration format for the written recording of adverse drug reaction cases has also undergone progressive revisions during its 10 years of development. Certain elements of information, such as the identities of all drugs which may have been involved in the reaction, at least a brief account of the reaction, and a basic description of the patient, are probably the essential items. Beyond this, if a valid evaluation is to be made, it is necessary to know about predisposing physicial conditions, such as an underlying disease, and other potentially hazardous factors, such as harmful products to which the patient may have been previously exposed. Innumerable other possible contributing factors could be listed. From a practical standpoint, however, it has been found that if the case-reporting format is sufficiently comprehensive to include all of the items which are desired, it becomes so involved that cooperation and interest in the reporting of individual cases will rapidly diminish. It is the current concept that the report form now being utilized contains what is perhaps the minimum quantity of information that can be used as a basis for a realistic evaluation.

During the course of this work, numerous sources of data have cooperated in providing case reports, and these are listed in Table I. The hospitals that have been selected for contracts which authorize monthly reporting are primarily those with a teaching affiliation and for the most part have in excess of 300 beds. While these are not rigid criteria for participation, it has been found through experience that institutions not having a full-time house staff or teaching programs find difficulty in organizing the procedures that are required for the collection of data to make the program productive. Exceptions to the usual bed capacity requirement are also made in the instances of hospitals primarily concerned with acute illnesses or

Table I. Sources of Data

I Hospital programs
- A. History of the programs and current status
- B. Contract (civilian) hospitals—90
  1. University affiliated
  2. 300–500 bed hospitals with teaching programs
- C. Federal hospitals
  1. U. S. Army hospitals
  2. U. S. Navy hospitals
  3. U. S. Air Force hospitals
  4. U. S. Public Health Service hospitals
  5. Veterans Administration hospitals

II Food and Drug Administration—field investigators
III National Institutes of Health
IV Scientific groups
- A. American Medical Association
- B. American Dental Association

V Pharmaceutical industry
VI Published literature
VII World Health Organization
VIII State departments of health
IX Armed Forces Institute of Pathology
X Research studies

in any institution, such as pediatric hospitals, where the length of patient stay normally is below the average. It has been found also that the designation of an individual person to be in charge, preferably someone with specific interest in pharmacology, is mandatory for the success of the program. Printed guidelines for reporting are published and provided in quantity to all participating institutions.

Through agreements with each of the surgeons general, military and other federal hospitals participate in this work in much the same manner as the hospitals cooperating under contracts. Payments are, of course, not made to federal institutions. The number of reports received monthly from all hospital sources now exceeds 1000. A list of the institutions currently engaged in this work is available in another Bureau of Medicine publication, "FDA Adverse Drug Reaction Reporting, Participating Hospitals."

Since the passage of the 1962 Kefauver-Harris amendments, there has been a requirement that adverse effects coming to the attention of pharmaceutical manufacturers must be included in reports which are submitted to the Food and Drug Administration. Of particular interest at this time is the new requirement that the standard Drug Experience Report form must now be utilized in the submission of these reports. This, of course, serves to outline the information which is desired in these reports, and consequently to aid in standardizing the submissions.

Since the large majority of reports indicate that at least several drugs had been administered at the time when a reaction occurred, the possibility of drug interaction is another basic factor which must always be considered. To attempt an objective evaluation, the approach must also be taken that any single drug in the series which was given, or that any possible mathematical combination of agents, acting as synergists or antagonists, could collectively be a group of offending agents. Because of these, and numerous other complicating factors, a preferable approach is perhaps to consider each case as a "suspected" adverse reaction, or in the more current terminology, a report of a "drug experience." Building, therefore, on a series of suspected or assumed causal relationships, a sufficient number of reports can be compiled to indicate trends of reactions as being associated with a drug, or even with combinations of drugs.

A basic question to be considered at this time, however, is how the actual evaluations, judgments, or ratings are presently made on the individual cases after they are received by FDA. First, it should be stressed that it is mandatory that all such evaluations of adverse drug reaction reports must be made by physicians. The reports for the most part have either originated from physicians or been developed with their cooperation, and can only be properly interpreted at a comparable level of clinical judgment. Due to the wide use of diagnostic synonyms and abstract inferences that are reflected through patient and disease descriptions, attempts at automated interpretation have not proven to be satisfactory. The complete review of each case by a medical officer is always preferred and has been the standard practice in the Bureau of Medicine.

In presenting a description of the evaluation procedures, the areas in which critical judgments must be made can be divided into three major groups. The first of these includes the documentation, or an assessment of the authenticity and completeness shown in the presentation of the report. The evaluating physician must here make a determination in regard to the sequential order of the events as described, the feasibility of the data and the adequacy of the information in providing a sufficiently comprehensive presentation. As a second analysis he must make a second assessment of the possibility and/or probability that the events as described could or could not have resulted in the suspected drug reaction. It should again be pointed out that this causal relationship need not be unquestionably established by either the source or the evaluator for the report to be of significance and value to the Bureau of Medicine. The third parameter for judgment is the determination of the potential significance of the individual report.

With the rapid accumulation of data in the field of adverse drug reactions, it became essential that automation be used to augment the physician's work by means of the rapid storage and retrieval of information. For this reason, computer processing has been incorporated into this work within the Bureau of Medicine. Facilities now exist for storing the completed material on computer tape, which provides extended search capabilities. As a major task in establishing this system, a dictionary of adverse reaction terms needed to be created, and was put into routine use during the past year. Sample introductory pages of this dictionary, which illustrate the primary categories (system-organ oriented) and the secondary (special-search oriented) categories are shown in Table

Table II. FDA—Dictionary of Adverse Reaction Terms

Volume I

Primary categories: (system-organ oriented)	Secondary categories: (special-search oriented)
(1) Body as a whole	(1) Addiction
General	(2) Efficacy lack
Regional	(3) Endocrine
(2) Cardiovascular system	(4) Hemorrhage
General	(5) Hypersensitivity
Cardiac	(6) Idiosyncracy
Vascular	(7) Immunologic impairment
(3) Collagen (connective tissue) disorders	(8) Injection-site reactions
(4) Digestive system	(9) Neoplastic
(5) Endocrine system	(10) Neurotoxic
(6) Fetal disorders	(11) Parasympatholytic (anticholinergic)
(7) Hemic and lymphatic systems	(12) Parasympathomimetic (cholinergic)
(8) Metabolic and nutritional disorders	(13) Photosensitization
(9) Musculo-skeletal system	(14) Poisoning, accidental
(10) Neonatal and infancy disorders	(15) Poisoning, intentional
(11) Nervous system	(16) Potentiation (synergism)
(12) Psychiatric disorders	(17) Sympatholytic (anti-adrenergic)
(13) Respiratory system	(18) Sympathomimetic (adrenergic)
(14) Skin disorders	(19) Systemic effect
(15) Special senses	(20) Teratogenic effect
(16) Urogenital system	(21) Thrombo-embolism
Urinary tract disorders	(22) Withdrawal syndrome
Female genital disorders	
Male genital disorders	

Table III. Reaction Terms

Term	Primary Category (System-Organ)	Secondary Category (Special Search)
ABDOmen MIMICking ACUTE	BODY/REG/ABDO	
ABDOminal PAIN	BODY/REG/ABDO	
Includes: ache		
cramp		
discomfort		
distress		
ABDOminal TENDERness	BODY/REG/ABDO	
Includes: soreness		
ABORTion (NOS)	UG/FG/PREG	(See Fetal Category for use of suffix ABORT)
ABORTion	UG/FG/PREG	(See Fetal Category for use of suffix ABORT)
Specified: COMPlete		
INCOMPlete		
MISSED		
THREATened		
ABSCESS	(SPCS)	(WS) IJCN
ABSCESS STERILE	(SPCS)	(WS) IJCN
Includes: cold abscess		
absorption rapid	(See SYSTEMIC EFFECT)	
absorption systemic	(See SYSTEMIC EFFECT)	
abstinence syndrome	(See WITHDRAWal SYNDrome)	

II. A sample page, depicting the type of reaction terms which are included, is shown in Table III. To implement the processing of material for storage, a coding sheet was also developed (Figure 1). This has sections that are routinely completed both by clerical personnel and medical officers. Of particular value in this coding process is an accession number which denotes the date that the report was received, the specific origin of the report, and a reference denoting whether this report was one of a series pertaining to a particular case. For coding purposes, the entries requiring the critical interpretation and judgment of data by medical officers are delineated into the categories which are shown. These include an assessment of the cause or relationship, the possibility of interaction, an evaluation of the severity, a conclusion regarding the outcome of the reaction, an assessment of the adequacy of the data, and a final rating that denotes the immediate importance or significance of the particular case. The pharmacological categories which are used in the processing are shown in Table IV. These groups represent only one of the many classifications that could have been employed, but they have been found effective for our particular objectives. The data items which are currently included in this processing are not only of value for making initial determinations, but also provide the future capacity of the system for completing epidemiologic research studies. These specific entries are as shown. The particular capabilities of the drug experience information system are indicated by the present end-products listed in Table V, these being the capacity for making highly selective searches and the bi-weekly and monthly alert reports. Additional products will subsequently be developed. Examples of the searches that can be requested and of the computer-generated monthly summation reports are:

> Reports of all thrombo-embolic events associated with oral contraceptives; sort by trade name of drug; sort by body system categories and specific thrombo-embolic sites; sort by 5-year age groups; sort by year of occurrence.

Table IV. Classification of Drugs According to Pharmacologic Activity

	Code Numbers
Local Anesthetics	72:00
Histamines and its Antagonists	4:00
Histamines	4:02
Antihistamines	4:04
Motion-sickness and anti-emetic agents (exclude phenathiazines see 28:16)	4:06
Anti-Infectives	8:00
Anti-arthropod drugs	8:02
Anti-protozoal agents	8:04
Anti-fungal drugs	8:06
Anti-helmintics	8:08
Antibiotics	8:12
Nitrofuran group	8:14
Anti-acid fast drugs	8:16
Anti-viral agents	8:18
Disinfectants; antiseptics and surface active ingredients	8:20
Sulfones	8:24
Anti-Neoplastic Agents	10:10
Autonomic Drugs	12:00
Cholinergic agents	12:04
Ganglionic blocking agents and smooth muscle relaxants	12:06
Cholinergic blocking agents	12:08
Ergots and derivatives	12:10
Adrenergic agents	12:12
Anorexogenic agents	12:12:02
Adrenergic blocking agents	12:16
Cardiovascular Drugs	24:00
Drugs affecting cardiac output and rhythm	24:02
Xanthine derivatives	24:04
Coronary and peripheral vasodilators	24:12
Sclerosing agents	24:16

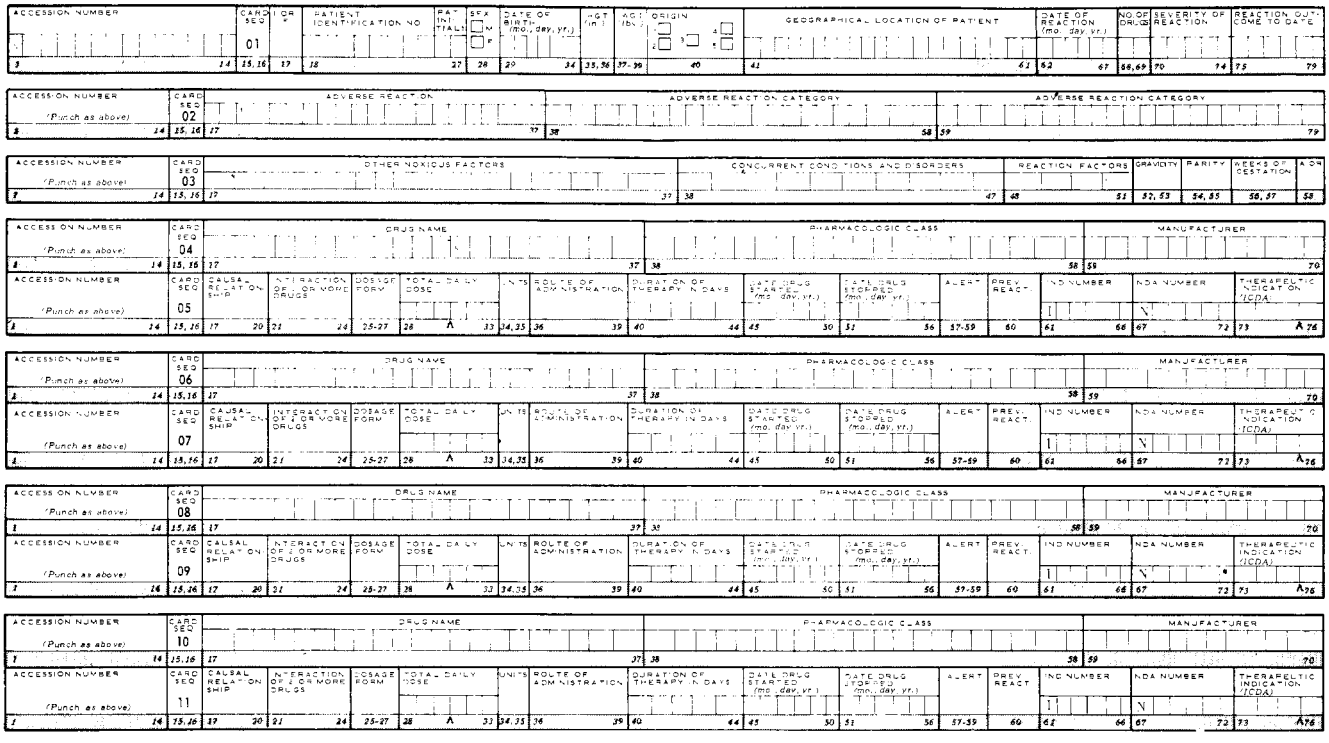

Figure 1. Coding sheet (for explanation see text)

All reports of hepatotoxicity associated with penicillin; sort by type of penicillin; sort by type of liver reaction.

All anticholinergic reactions reported in association with chlorpromazine, trihexyphenidyl and imipramine, with each drug when used alone and when used in any combination.

All reports of accidental poisoning from outdated drugs; sort by name of drug, nature of reaction and outcome of reaction.

The results derived from this system have already demonstrated their potential to the Bureau of Medicine.

All of the information which has been described in the preceding discussion has been collected on the basis of isolated case reports. In an effort to augment this by determining the incidence of adverse drug reactions in the population, and to gain other knowledge concerning the epidemiological aspects of reactions, several research studies have been initiated by the Bureau of Medicine. From these carefully designed studies, it is anticipated that a continuing accurate monitoring of hospital populations for adverse effects can be made and the occurrence of adverse reactions can be directly related to comprehensive drug usage data. The results from each epidemiologic study will be processed for automated analyses. Under one of the projects, surveillance of individual drugs can also be accomplished.

The final overriding consideration of the system is proper dissemination of information. The collection of large quantities of well-documented data, the careful analysis of these, and the development of unprecedented information all would be of little value without the proper dispersion of material. For this reason, the Bureau of Medicine has for a number of years distributed its journal entitled *Reports of Suspected Adverse Reactions to Drugs*. This publication includes a cross-section of reports that have been selected from among those received for a particular month. They are chosen on the basis of their general interest. It is hoped that within the near future both the content and distribution of this material will be expanded.

With the establishment of the continuing sources of adverse reaction data input, the computer system for rapid analysis, and the new capabilities for searches and dissemination, it is felt that much has been done toward initiating the answer to the question of drug surveillance. However, the problem of acquiring the wide scale interest and effort to totally develop and disperse all of the information that is desired and needed for the assurance of complete safety in the prescribing of therapeutic agents, still remains.

Table V. Drug Experience Information System

Present products:

(1) Search capability for adverse reaction information
(2) Bi-weekly Alert Report
(3) Monthly journal, *FDA Reports of Suspected Adverse Reactions to Drugs*

Future products:

(1) Periodic cumulative reports by drug group to satisfy the interest profiles of Bureau staff
(2) Epidemiologic research capability
(3) Proposed Drug Experience Review for external publication