5.
Current Activities

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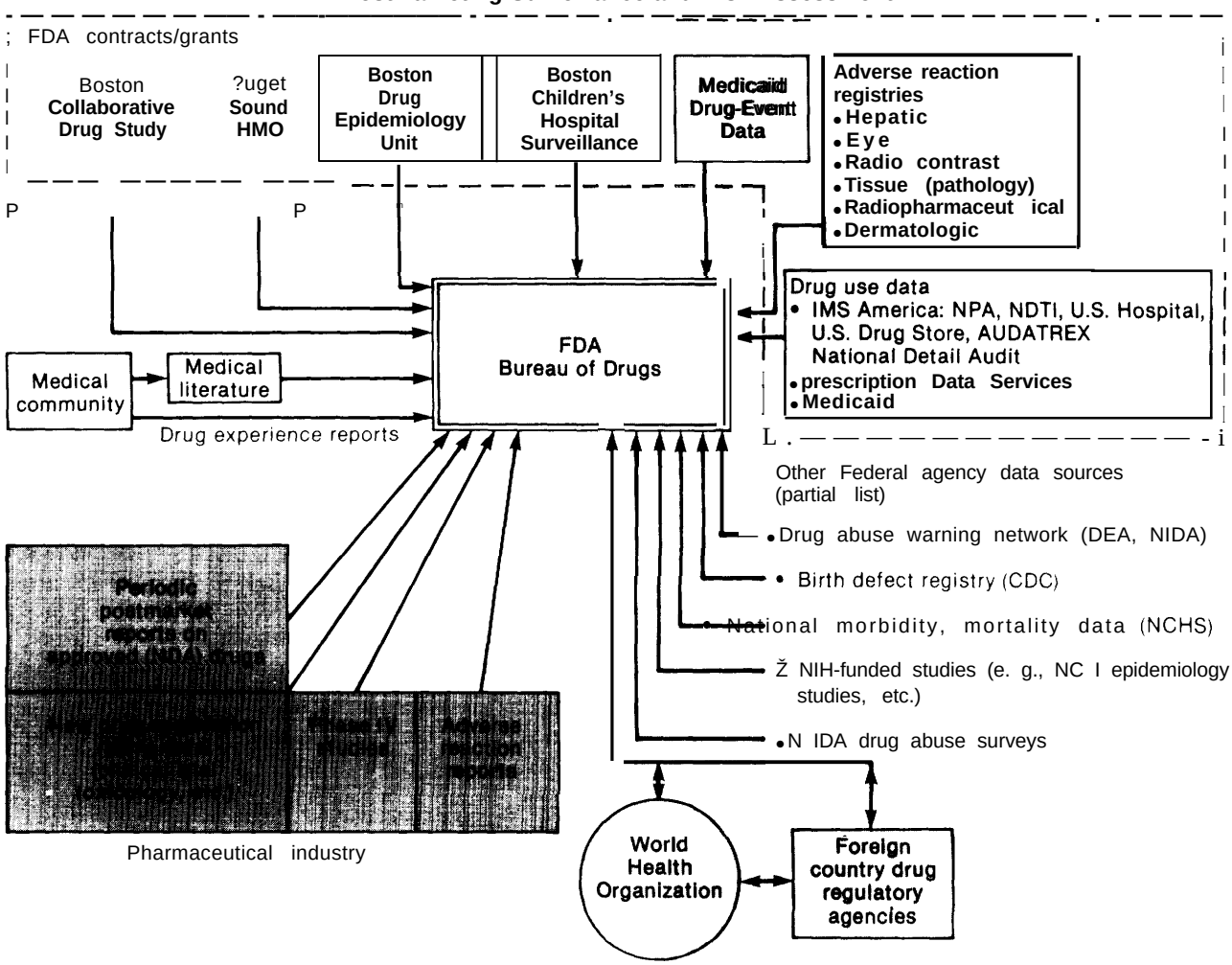
The following discussion suggests only some of the kinds of activities and resources that can contribute to postmarketing surveillance.

The Food and Drug Administration (FDA) obtains information on the postmarketing status of drugs from four main sources: 1) pharmaceutical manufacturers, 2) FDA contracts and grants, 3) other governmental agencies, and 4) international centers such as the World Health Organization (WHO). Figure 3 summarizes the data sources available to FDA in its monitoring of drugs.

Pharmaceutical manufacturers are required to report all adverse reactions regardless of whether a causal connection is believed to exist between the drug and the symptom (CFR 21.310.301). Most of these adverse events are reported by physicians, and many manufacturers have routine

Figure 3.— Drug Experience/Epidemiologic Sources Available to FDA for Postmarketing Surveillance and Risk Assessment



SOURCE U S Food and Drug Administration

procedures for responding to such spontaneous reports. A number of companies also carry out "product support studies" to interest physicians in their products, and to defend a drug if it is suspected of causing an adverse effect, or if questions are raised about its therapeutic value (12).

Manufacturers may also have to conduct a "phase IV" postmarketing study as a condition of marketing approval. Two examples of such research, that on streptokinase and cimetidine, were described in chapter 4.

Some manufacturers are also attempting to develop their own surveillance programs. For example, Upjohn used group medical practices to form a pharmacy-based cohort for prospective observational studies of selected drugs in order to establish a large registry of patients to identify and analyze important medical events through follow-up patient questionnaires **(5).**

FDA grants and contracts cover a number of activities. Voluntary reporting by physicians to medical journals and directly to FDA is augmented by several specialized registries:

- The National Registry of Drug-Induced Ocular Side-Effects collects data from U.S. ophthalmologists on drugs and their effects.
- The Registry of Patients Exposed to Radiopharmaceutical Drugs collects information from a random sample of hospitals licensed to practice nuclear medicine. All patients exposed to radiopharmaceuticals are registered, and adverse effects are reported.
- The Registry of Hepatic Toxicity to Drugs collects data on drug reactions that affect the liver.
- The Registry of Dermatological Reactions to Drugs, administered by the American Academy of Dermatology, was recently initiated to collect data on reactions affecting the skin and on reactions to dermatological drugs.

FDA purchases data from private organizations to estimate the actual population using a drug. One use of this data might be to determine whether patients exposed to a drug have an increased risk of experiencing an adverse effect. Another use might be to estimate the number of patients who would be using a new drug to help decide whether a postmarketing study of the drug would be needed.

For example, FDA's Division of Drug Experience contracted to use the Medicaid Medical Information Systems of Michigan and Minnesota to link individual prescription and diagnostic claim files for 1.2 million patients, to access and tabulate the data, and to provide FDA with online terminal access to the data, to update the patient profiles on a quarterly basis, and to provide specified reports. The Division of Drug Experience plans to use this Medicaid data base for the following purposes: 1) investigation of what FDA considers high-priority issues on adverse reactions, 2) development of data on drug utilization, **3)** development of a screening system for hypothesis generation of unsuspected adverse effects, and 4) studies to describe and validate the usefulness of the data base (25). Table 9 summarizes the anticipated uses of this data base. Table 10 identifies this and other data sources available to FDA for estimating actual populations of drug users.

In addition to using the Medicaid data from Michigan and Minnesota to develop cohorts for studies of drug use, FDA contributes to the support of several ongoing surveillance programs, some of which include data collected from other countries (e. g., Great Britain, New Zealand, Israel).

The Boston Collaborative Drug Surveillance Program (44) has accumulated data on the past hospitalizations of more than **50,000** patients. This data base is still useful for evaluating older drugs. The program also uses current data from the 280,000 members of the Group Health Cooperative of Puget Sound (Washington State) and the data files of the Commission on Professional and Hospital Activities-Professional Activity Study in Ann Arbor, Mich. These data sources are useful for evaluating new drugs.

The Drug Epidemiology Unit at the Boston University Medical Center conducts case-control studies (e.g., on birth defects), and also intensively monitors pediatric hospital patients in collaboration with the Children's Hospital Medical Center in Boston.

Table 9.— Potential Uses by FDA of Medicaid Data From Michigan and Minnesota

General descrlpt!on of study	General use	Example	Anticipated future impact
Drug utilization			
1. Overall characterization of drug use by Medicaid population	Cross-validation with data on drug use. Identification of potential high drug exposure problem areas,	Oral contraceptive use. Use of isoxsuprine in pregnancy. High codeine use,	Confirmation of suspected problems (e.g., unlabeled uses). Label changes. Publication in medical literature, *ADR Highlights.*
2. Demographics of drug use	Inappropriate drug use along demographically defined high-risk groups.	Association of high-dose estrogen oral contraceptives with older premenopausal women.	Labeling changes to indicate demographically defined high-risk groups, *ADR Highlights.*
3. Drug use combinations	Inappropriate use of interacting drugs in individuals.	Use of steroids in individuals on oral hypoglycemic agents.	Labeling changes and publications to warn against untoward drug combinations that appear prevalent. *ADR Highlights.*
4. Drug use in diseased individuals,	Inappropriate use of drugs in certain risk groups defined by disease	Use of indomethacin in individuals with history of GI bleeding.	Publication to warn of apparent prevalent misuse of drugs. Labeling changes as indicated. *ADR Highlights.*
Drug adverse effects			
1. Relative prevalence/incidence of known adverse effects.	Current rates of ADRs are known only for common drugs— this data base allows definition of relative risk for most ADRs (except rarest)	Relative rate of hepatic disorders in erythromycin (estolate v, other salt users). Relative rate of heart failure in disopyramide v. quinidine or procainamide users (alone and/or in combination).	Labeling changes, Publications (*ADR Highlights* and/or medical literature). General ability to place in perspective ADRs due to disease v. drug.
2, Rate of recognized drug adverse effects.	Supplement to spontaneous reporting system. Source of information on perception and reporting of ADRs.	Estimates of rate of reporting (or physician recognition) of ADRs such as hepatitis, etc.	Also serves as information base for insight into perceived drug-induced disease.
3. Identification of drug adverse effects by means of rate ratios from case control or cohort modules.	Identify possible drug-induced disease for further investigation.	Association of laryngospasm with NSAID.	Stimulate further research using other data bases. Labeling change/warning.
4. Detection of acute drug-induced disease from temporal clustering of events following exposure.	Identify possible drug-induced disease for further investigation.	Association of phenylpropanolamine with CVA.	Stimulate further research using other data bases.

SOURCE U S Food and Drug Administration

Table 10.—Data Sources Available to FDA for Estimating Actual Populations of Drug Users (current and future)

1. *IMS America,* Ltd.
- **National Prescription Audit—survey of prescriptions dispensed at pharmacies**
- **National Disease and Therapeutic Index—survey of physician-patient contacts listing diagnoses and therapies (not prescriptions)**
- **U.S. Hospital —survey of bulk sales to hospitals**
- **U.S. Drug Store— survey of sales to drug stores**
- **Audatrex —sample of physicians and their prescribing habits over time**

2. Prescriptlon *Card Service* (PCS)—data on third-party paid prescriptions, usually union, with national estimates

3. *Medicaid* (exploratory) -data will be available on all drug use, linked to clinical events, for 1.2 million patients in Michigan and 0.25 million patients in Minnesota

Other than bulk sales to hospitals, there are no current national samples of hospital drug use.

SOURCE: US **Food and Drug Administration**

Other governmental agencies also collect data that may be of use to FDA:

- The National Center for Health Statistics collects a wide variety of health data. FDA has asked the center to collect drug data on death certificates, and also to investigate the possibility of collecting drug information in its National Ambulatory Medical Care Survey.
- The National Centers for Disease Control have a Birth Defects Monitoring Project to alert for possible increases in the incidence of birth defects. This project could help detect birth defects due to drugs taken during pregnancy.
- The National Cancer Institute's Environmental Epidemiology Branch sponsors case-control studies to investigate associations between environmental agents (including drugs)

and the development of specific types of cancer, using data from prepaid health plans.
- The Drug Enforcement Agency and the National Institute on Drug Abuse survey emergency rooms and coroners through their Drug Abuse Warning Network to monitor drugs that are abused and their association with adverse reactions.

International monitoring activities include WHO's Program for International Monitoring of Adverse Reactions, which has 23 participating countries. FDA's Division of Drug Experience is the designated National Monitoring Center for the United States. It exchanges reports with WHO, each organization summarizing the adverse drug reactions (ADRs) added to their systems in the previous year. The purpose of WHO's monitoring program is to increase the probability of detecting effects that might be overlooked by individual countries. Its chief value to the United States is in providing information about drugs that are available elsewhere in the world, but are not yet marketed here.

Drugs may be introduced and used abroad for a number of years before they are approved in the United States. In fact, the more rapid approval and introduction of drugs in other countries has been one of the reasons behind the charge that the U.S. drug approval process is too slow, keeping valuable drugs from the market. However, this earlier introduction of drugs in other countries also uncovers adverse effects and helps modify the indications for use before the drug is released in this country, because the international community can pool and share information on the effectiveness, safety, and use of drugs.

Currently, FDA's Division of Drug Experience receives about 12,000 adverse event reports annually from industry (reports that are mandatory), the medical community, and others. About three-quarters (60 to 80 percent) of these reports come from manufacturers, who, in turn, receive most of their reports from physicians. Table 11 summarizes the sources of adverse event reports for 1972-78, and table 12 identifies individual sources for fiscal year 1978. The relationship between these reported effects and drug use varies greatly. For example, in 1977, approximately 150 reports were on deaths that were "definitely" or "probably" drug related, but more than 400 other reports were not clearly drug related or due to overdoses (63).

The reports of the Division of Drug Experience have been computerized and, depending on their accuracy and completeness, can be screened or retrieved in the following classifications (63):

- by drugs or drug class related to the suspected adverse reactions;
- by adverse reaction related back to suspected drugs;
- by one of four cause-and-effect relationships: definite, probable, possible, and remote;
- by alert "yes" or "no," meaning that the reaction is or is not novel, unanticipated, previously unreported, or not mentioned in the product labeling;
- by demographic data;
- by source of report;
- by possible interactions; and
- by outcome of reaction.
- Retrieval can also extend to original reports on microfilm.

Table 11.— Number and Percentage of FDA's Adverse Event Reports by Source, 1972-78

Source	1972	1973	1974	1975	1976	1977	1978
Manufacturers	**9,750 (76.0%**	**6,700 (62.20/o)**	**6,807 (70.1 %)**	**8,097 (75.2%)**	**7,664 (63.80/,)**	**8,945 (71.8%)**	**9,143 (81.2%)**
Physicians/other health professionals	2,189 (1.8°/0)	985 (20.30/,)	699 (10.1 "lo)	2,138 (6.6%)	1,862 (17.8%)	1,335 (15.0%)	(11.90\o)
Hospitals	2,559 (20.0%)	1,690 (15.8%)	1,306 (13.5°/0)	(8.7%)	(8.7%)	859 (6.9%)	423 (4.0°/0)
All other	297 (2.2%)	182 (1.7%)	611 (6.3%)	917 (8.5%)	(9.7%)	(6.3%)	358 (3.7°/0)
Totals	12,837	10,761	9,709	10,756	12,012	12,459	11,259

SOURCE A Ruskin and C. Anello, "In *Monitoring* for *Drug Safety,* W. H, W, Inman (cd.) (Philadelphia' J B. Lippincott Co , 1980)

Table 12.—Number of FDA's Adverse Event Reports by Specific Sources, Fiscal Year 1978

Source	Number of reports
Manufacturers	9,143
Physicians/other health professionals:	
Physicians	1,199
Pharmacists	105
Dentists	31
Hospitals:	
Federal	182
Non-Federal	241
All other:	
Consumer	24
District of Columbia,	68
Methadone Centers	266

SOURCE US Food and Drug Administration

These reports are supplemented by a separate but parallel literature search by FDA of l40 journals (in English) that focuses on serious adverse effects not mentioned in the drug labeling. This literature search is published monthly in FDA's "Current Drug Experience Literature."

FDA has begun to use the computerized file of ADRs in a screening method (screening of adverse reactions, or SOAR) to assist its clinical reviewers in identifying previously unsuspected adverse reactions that might warrant in-depth clinical investigations. The SOAR method compares a drug's proportional share of specific adverse reactions (relative to its therapeutic class) with its respective proportional share of drug use for a particular time period. The latter data are derived from national estimates of the total amount of a particular drug dispensed during a 3-month period, divided by the amount that would be used per day. The resulting number would represent the potential number of days a patient was exposed to the drug. An in-depth review may be considered when the proportional share of reported adverse events relative to the proportional share of drug use is greater than that predicted.

FDA's postmarketing surveillance of ADRs is not a surveillance "system" per se, but rather a group of potentially related activities. Many of these activities are not exclusively carried out for FDA's monitoring program. For example, the intensive monitoring programs to which FDA contributes support also collaborate in large-scale clinical trials of drug efficacy that are sponsored by the National Institutes of Health. Many of the voluntary reporting systems, such as the specialized registries (e. g., those for ocular side effects, dermatological reactions, and hepatic toxicity), also have multiple purposes.

FDA's monitoring is based primarily on voluntary reporting. The agency is just beginning to establish the data bases needed to confirm or reject those possible associations between drugs and adverse reactions that are first identified through the various kinds of voluntary reporting.

These observations point to the following areas of inquiry:

First, how can FDA's coordination of its postmarketing surveillance activities be improved? Currently, it is difficult to evaluate the monitoring activities in which FDA is involved, because their emphasis so far has been on collection of data, not on its final use; thus, the potential uses of the data are largely unrealized.

Second, are FDA's own voluntary reporting and data-gathering programs and the other, more specialized drug reaction registries it supports appropriately targeted and sufficiently utilized? A recent General Accounting Office reevaluation of FDA's voluntary reporting system criticizes FDA's tardiness in evaluating and using these reports (29). The relative value of the various specialized registries to FDA's monitoring responsibilities is not known.

Finally, should FDA be responsible for testing the hypothesis that a drug maybe associated with an adverse reaction, or should that be the responsibility of the drug's manufacturer? FDA could support the formation of various prospective cohorts and coordinate that activity with the information FDA receives from voluntary reporting. But FDA's role could also be limited to helping identify the most important drugs to monitor, with the actual monitoring performed by the drug's manufacturers.