3
History and Objectives of Postmarketing Surveillance

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In the 1960's, at least two serious drug reactions were observed in many patients. The drug thalidomide, taken worldwide, led to limb deformities (phocomelia) in the newborns of those mothers who took the drug while pregnant. Less known, and almost exclusively observed in Japan, was the optic nerve damage (subacute myelo-optic-neuropathy) and other adverse effects from the drug clioquinol, over which almost 4,000 civil suits were still pending in 1979 (68). And in Great Britain in the early 1970's, more than 4 years after the drug had been introduced there, the "practolol syndrome" was uncovered. Practolol, a drug used to treat cardiovascular disease, was eventually found to cause skin rashes, eye lesions, hearing impairment, and sclerosing peritonitis (56), with deaths occurring in about 2 percent of reported cases (37).

Great Britain, with its national health system, already had a voluntary reporting system (37). The national health system had instituted the use of "yellow cards" for reporting suspected adverse drug reactions (see fig. 1). As a guide to reporting, certain drugs are marked the first 4 years after they are marketed with an inverted black triangle in a booklet, the Monthly Index *of Medical Specialties,* which is distributed to physicians and used as a source of information for prescribing drugs more frequently than any other publication. In 1976, a slip of yellow paper was inserted into prescription pads to remind physicians to report reactions, leading to a large and consistent increase in the rate of reporting. Many British drug companies now use the yellow card, and the yellow card system and reports from drug companies together yield 90 percent of all reports of suspected adverse drug reactions (ADRs) (see table 4).

The delayed discovery of practolol's adverse effects spurred efforts to improve postmarketing surveillance, and several international meetings quickly followed in Sestri Levante, Italy (20), Honolulu, Hawaii (33), and London (53). In Great Britain, efforts focused on "early detection of adverse drug reactions by recording all adverse events occurring in a specified number of patients for an appropriate period of time; endeavoring to avoid collecting masses of unusable data and minimizing costs" (75). Thus, the early impetus was toward monitoring new drugs for adverse effects through some type of program that would help fill the gap between identifying those adverse effects sufficiently common to be detected in the premarketing trials, and identifying those so rare that voluntary reporting after marketing is their most feasible form of monitoring. The proposed methods all centered around the prescribing practices of physicians, with the experience of their patients on new drugs being examined periodically through questionnaires to the prescribing physicians. Such methods of monitoring include registered release (17), recorded release (36), and monitored release (45,79).

More recently, the objectives of postmarketing surveillance in Great Britain have been expanded, though not implemented (35):

> The need for PMS [postmarketing surveillance] is not restricted to new drugs. Some of those already marketed for many years may increase the risk of chronic disease or may have long-delayed carcinogenic effects, as illustrated in the United States by the cases of vaginal adenocarcinoma in the adolescent female children of women who took diethylstilbestrol during pregnancy.
>
> PMS should also include assessment of efficacy, especially of long-term treatment. Very little is known of the *relative* merits of members of groups of drugs such as hypotensive or anti-diabetic agents, anti-rheumatics or psychotropic. Prescribers need to know the most effective treatment available just as much as they need to know the risks involved, but government drug regulatory authorities (DRAs) are reluctant to become involved in relative efficacy, and drug companies are not naturally inclined to invest in comparisons of closely related compounds which may not show their own product to be the best.

Figure 1.—Yellow Card Report Form Used in Great Britain

IN CONFIDENCE–REPORT ON SUSPECTED ADVERSE DRUG REACTIONS

1. Please report all reactions to recently introduced drugs and serious or unusual reactions to other drugs. (Vaccines should be regarded as drugs).
2. Record on the top line the drug you suspect of causing the adverse reaction.
3. Record all other drugs, including self-medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Do not be deterred from reporting because some details are not known.

NAME OF PATIENT (To allow linkage with other reports for same patient. Also give record number for hospital patient) | **SEX** | **AGE OR DATE OF BIRTH** | **WEIGHT**

DRUGS* (Give brand name if known) **ROUTE**	**DAILY DOSE**	**DATE STARTED**	**DATE ENDED**	**INDICATIONS**

● For Vaccines give Batch No.

REACTIONS	**STARTED**	**ENDED**	**OUTCOME** (e.g. fatal, recovered)

ADDITIONAL NOTES

REPORTING DOCTOR

Name

Address

Tel. No.

Signature

Date

Figure 1.—Yellow Card—Continued

REPORTING ADVERSE REACTIONS: GUIDELINES

DO NOT REPORT
1. Deliberate or accidental overdose
2. Overdose due to errors of prescribing or administration
3. Excessive but otherwise 'normal' effects of drugs whose dose has to be carefully titrated (e.g., insulin, hypotensives, anticoagulants)
4. Familiar relative overdose—excessive effect of a normal dose due to known predisposing factors (e. g., digoxin toxicity in presence of hypokalaemia; toxicity in patients with impaired renal function)
5. Inevitable side effects produced by known pharmacological activities of a drug (e.g., dry mouth with anticholinergic drugs, tricyclic antidepressants, etc.; and hyperuricaemia with diuretics)

REPORT ALL
1, Drug interactions—known or suspected
2, Reactions to new drugs marketed for less than 3 years
3. Totally unexpected or unexplained events (including death) which could be drug induced
4. Congenital abnormalities
5. Infrequent reactions causing significant morbidity even if well known

CHECK LIST FOR REPORTING (not comprehensive)

General	a. anaphylaxis b. all serious skin rashes c. all blood dyscrasias d. thrombosis associated with oestrogens or oral contraceptives
Gastro-Intestinal	a, jaundice b. malabsorption c, intestinal ulceration d. severe bleedlng
Cardiovascular	a. myocardial toxicity, e.g., unexpected arrhythmias (exclude digoxin) b. hypertensive reactions
Respiratory	a. brohchospasm b. non-infect!ve lung disease, e.g., pneumonitis, fibrosis
Nervous System	a. convulsions b. unexpected confusional states (hallucination or psychotic reactions) c. unexpected extrapyramidal effects (exclude phenothiazines and butyrophenones) d. peripheral neuropathy e. neuromuscular blockade f. myopathy and myalgia
Eye & Ear	all reactions
Endocrine	a. unexpected reactions b. amenorrhea c. infertility **Exclude** gynaecomastia, fluid retention, hypokalaemiaemia, hyperkalaemia, hypoglycemia, hyperglycemia, hyperuricaema porphyria (if produced by drugs known to have these effects)
Renal	ail nephrotoxicity **Exclude** urinary retention induced by diuretics or due to anticholinergic drugs
Joints	a. all arthropathies b. D. LE. syndrome

SOURCE Committee on Safety of Medicines. London

Table 4.— Percentage of Reports of Suspected ADRs in Great Britain by Class of Reporter and Method Used[a]

	Percentage of reports by class of reporter				
Method used	General practitioner	Hospital consultant	Hospital junior	Others (e.g,, coroner)	All reporters
Yellow card.	58.3%	6.30/o	9.7%	1.7%0	76.00/o
Drug company	6.2	4.5	2.9	—	13.6
Correspondence	1.7	0.8	0.4	4.6	7.5
Death certificates	0.2	—	1.3	0.9	2.4
Medical journal	—	0.2	0.3	—	0.5
All methods	66.40/,	11 .80/0	14.60/o	7.20/,	100.0%0

aBased on random 10 percent sample of approximately 12,000 recent reports up to June 1978

SOURCE W H W Inman (ed), "The United Kingdom, " In *&for? itoring for Drug Safety* (Philadelphia' J B. Lippincott Co , 1980)

Furthermore, an earlier suggestion linked postmarketing surveillance with restricted release of drugs (75):

> A case could be made for an immediate or restricted release system for the introduction of new drugs before their widespread use, half way between clinical trials and the monitored release proposals. Because of inevitable delays, it is possible that by the time 5,000-10,000 cases have been fully monitored by any of the above schemes, many more patients will have been exposed to the drug so that any serious adverse reactions in the monitored group are duplicated in those patients not fully monitored. The duration of the "restricted release" phase would depend on the drug and disease concerned. Monitoring of patients would continue, when appropriate, after the drug became generally available.

In the United States, the Food and Drug Administration's (FDA's) drug approval process was already under intense scrutiny in the early *1970's*. As a result of **1974** hearings before the Subcommittee on Health, Senate Committee on Labor and Human Resources, chaired by Senator Edward Kennedy (D-Mass.), the Department of Health, Education, and Welfare formed a Review Panel on New Drug Regulation. This panel, which convened in February 1975 and issued its report in May 1977 (16), addressed two issues: 1) whether the drug law requirements for premarketing testing unnecessarily delayed the availability of valuable prescription drugs, and 2) whether the drug industry exerted undue influence on FDA decisions. The panel concluded that there was insufficient evidence on the first question and no widespread improper influence. It also identified four categories of deficiencies in the regulation of drugs: 1) openness and public accountability, 2) FDA's science environment, 3) standards and procedures for premarketing approval, and 4) FDA's role in the postmarketing period (16,18).

Senators Kennedy, Javits, and others then introduced a bill in early 1978 to revise the drug provisions of the Food, Drug, and Cosmetic Act. A revised bill, S. 1075, the Drug Regulation Reform Act of 1979, passed the Senate in September 1979. However, a similar bill, H.R. **4258,** was not acted on by the House of Representatives. Included in the Senate bill were these proposed changes in existing law: 1) drug sponsors could be required to conduct postmarketing surveillance of a drug for up to 5 years; 2) a prescription drug could have its distribution limited if it could not otherwise be found to be safe and effective; 3) the standard for a drug's immediate removal from the market would be changed from the drug being an "imminent hazard to the public health" to the less stringent standard of "unreasonable risk of illness or injury to any segment of the population;" and 4) establishment of a "National Center for Drug Science. "

During this period, in a speech to the Pharmaceutical Manufacturers Association, Senator Kennedy suggested that a better system was needed for monitoring the use and effects of prescription drugs after they were marketed. As a result, the Joint Commission on Prescription Drug Use was established in 1976, funded largely by the drug industry, with the mandate to design a postmarketing surveillance system to detect, quantify, and describe the anticipated and unanticipated effects of marketed drugs, and to recommend a means by which information on the epidemiology of prescription drug use in the United States could be distributed regularly to interested parties. The Joint Commission issued its report in January 1980 with the following five conclusions and recommendations identified as its most important ones (see app. B for the complete list) (42):

1. A systematic and comprehensive system of postmarketing drug surveillance should be developed in the United States.
2. Such a system should be able to detect important adverse drug reactions that occur more frequently than once per thousand uses of a drug, to develop methods to detect less frequent reactions and to evaluate the beneficial effects of drugs as used in ordinary practice. New methods will have to be developed for the study of delayed drug effects, including both therapeutic and adverse effects.
3. An integral function of the postmarketing surveillance system should be to report the uses and effects of new and old prescription drugs.
4. Recognizing the progress that FDA has made in the area of postmarketing drug surveillance in the last 3 years, the Commission recommends that PMS [postmarketing surveillance] should be a priority program of the FDA and that the FDA should continue to strengthen its program in this area.

5. A private, nonprofit Center for Drug Surveillance (CDS) should be established to further the development of a postmarketing surveillance system in the United States. This center should foster cooperation among existing postmarketing surveillance programs, develop new methods for carrying out surveillance, train scientists in the disciplines needed for doing postmarketing surveillance, and educate both providers and recipients of prescription drugs about the effects of these drugs.

In 1976, the year in which the Joint Commission was formed, an interagency agreement was signed between FDA and the Experimental Technology Incentives Program (ETIP) at the National Bureau of Standards of the Department of Commerce. The purpose of ETIP was to provide incentives or reduce barriers to technological innovation through changes in the regulatory process. ETIP's agreement with FDA was to jointly fund a program to determine if improvement in postmarketing surveillance could help reduce the regulatory requirements of the premarketing period, principally those of phase III of the investigational new drug process and those of the following new drug application process. The specific experiment was to develop postmarketing surveillance systems and a method of managing and evaluating the reform (11).

The project concentrated on collecting data to design such systems, and issued a status report in 1981 (12). Another report will be issued by the project in **1982.** FDA has assumed most of the funding, and the Department of Commerce was to phase out ETIP in 1982. FDA is continuing the activities originated or stimulated by the program (see ch. 5).

A Commission on the Federal Drug Approval Process was convened in mid-1981 to examine how FDA's procedures for the approval of new *drugs* can be expedited without compromising public safety; it is to also make recommendations on the development of cost-effective postmarketing surveillance to guarantee the quick withdrawal from the market of drugs that cause significant adverse effects. The commission had its genesis in a joint hearing held in April 1981 by the House Science and Technology Committee's Subcommittee on Natural Resources, Agriculture Research, and Environment and its Subcommittee on Investigations and Oversight. The commission's first meeting was held in July 1981, and its report was to be released in late 1982.

FDA is also examining specific ways to speed up the drug approval process. It is reviewing past phase 111 trials to see if longer trials or those with large sample sizes have contributed useful information beyond that obtained in phase II and early phase III testing. Past postmarketing studies that FDA has required are also being reviewed to see if they provided the information that was originally sought. FDA data on approval time, validated by interviews with FDA and the manufacturers, are being reviewed for factors that may slow the approval process. And, as a pilot test, an FDA committee is reviewing the pharmacologic and clinical data on selected drugs at the end of phase II testing, and will make recommendations about the best time to gather additional safety information (e.g., phase III v. the postmarketing period) (11). FDA Commissioner Hayes has been quoted as saying that one possible methodological change is to accept foreign data in the premarket approval process (67). These activities have resulted in proposed new rules for new drug regulation (47 *Federal Register,* pp. 46622-66, **Oct.** 19, 1982). In March 1982, the FDA Commissioner began a related reorganization by merging the Bureau of Drugs with the Bureau of Biologics, and replacing the Director of the New Drug Evaluation Division. The merged bureaus have since been designated the National Center for Drugs and Biologics.

Finally, in a related development, the Senate passed by a voice vote, in the first session of the 97th Congress, the Patent Term Restoration Act of 1981 (S. 255). The bill would restore to the term of a patent the time lost in complying with the Government's premarket testing and review requirements, up to a maximum of 7 years. Patented products eligible for extension would not be limited to human drugs, but would include "human drugs and biological, antibiotic drugs, animal drugs and biological, food additives, color additives, pesticides, other chemical substances, medical devices, and any other product subject to Federal premarket requirements"

(72). In September 1982, the House of Representatives voted on the bill under suspension of its rules. Under such conditions, a two-thirds vote was required for passage, and although the bill received a majority of the votes, it fell just short of the two-thirds majority needed.

Thus, in the United States, the issue of postmarketing surveillance has involved more than identifying the serious adverse effects of newly introduced drugs. It has also led to the recommendation to monitor all drugs for their effectiveness and appropriate use by patients and physicians. In addition, improvements in postmarketing surveillance have been linked to changes in the drug regulatory process. Proponents of more rapid drug approval claim that phase III testing (e.g., the chronic trials) adds little to the data collected in phase II, and that, as a consequence, phase 111 testing could be curtailed or shifted to the postmarketing period. On the other hand, those concerned about drug deficiencies discovered after drug approval point out that FDA has limited options once a drug has been released. Since FDA lacks authority to limit drug distribution or use, it can only try to remove a drug from the market, if such action appears appropriate.