Adverse Drug Reactions—A Continuing Problem

During the past year, there have been several major drug recalls and withdrawals from the market. We are referring here to those cases involving toxicity and adverse reactions associated with the active ingredient itself, rather than recalls resulting from product tampering, faulty manufacturing of dosage forms, or other considerations relating to the quality of the drug product.

Two of the more publicized such recalls were for benoxaprofen (Oraflex) and zomepirac (Zomax).

Various interested observers of the national pharmaceutical scene have drawn a variety of conclusions from this rash of recalls. The conclusions have been diverse and, in many cases, filled with conjecture and hypothesis. As such, they have ranged from "look how poorly the new drug approval system is working to allow all these unsuitable drugs to be placed on the market" to the other extreme, namely, "look how well the new drug approval system is working since these adverse reactions were identified and the drugs pulled off the market." But in any event, everyone seems agreed that there are, and will continue to be, instances where significant drug toxicity does not become evident until the product involved goes into general distribution and thereby experiences widespread use in patients.

Given that situation, a problem with a drug will only come to light if a sufficient number of physicians, pharmacists, or other health care practitioners in a position to monitor patient reaction to therapy (*a*) note that a patient has suffered an untoward effect, (*b*) make the critical mental connection between drug and untoward reaction, and (*c*) duly report it to the manufacturer and/or the Food and Drug Administration.

Unfortunately, however, this sequence often does not occur. In fact, the usual pattern is that—*after* the first such clinical experiences are reported in the letters columns of medical journals—there is then a flurry of similar reports from practitioners who had previously failed to make the mental association in patients they had treated earlier. But aside from efforts to make practitioners more alert, to sharpen their association skills, and to urge them to be conscientious in reporting adverse reactions, there seems to be little that can be done to improve the reporting system from the field.

Moving on, then, after adverse reaction reports have been filed with FDA, what happens next?

The apparent general supposition on the part of the public, members of Congress, and many members of the health care professions is that an alarm is immediately triggered, the FDA springs into action, and the drug is immediately whisked off the market. In essence, a reaction is assumed that would be comparable in speed and effectiveness to that expected from our national military defense in the event of a nuclear attack.

Obviously, however, even under the best of circumstances and even under ideal operating conditions, no adverse reaction system will work that well.

So, how well is the present FDA system working?

The answer appears to be: Not very well. In fact, rather poorly, indeed.

A little over a year ago, on March 8, 1982, the watch-dog agency in the federal government—the General Accounting Office, or GAO—released a report on 21 selected prescription drugs and found that it took an average of five months for adverse drug reaction (ADR) reports just to be entered into the computer files of the FDA's Division of Drug Experience.

In summarizing their findings, the GAO said: *"Based on a sample of almost 2,000 adverse reaction reports submitted by manufacturers, (1) 42% of these reports never reached the Drug Experience Division, (2) an additional 14% had been received but either had not been evaluated or were in a backlog waiting to be entered into the system, and (3) reports that had been entered into the system [were entered] an average of five months [after they were received at FDA]."*

This was not the first time the GAO had delved into FDA's ADR reporting system. In fact, it was a follow-up to a 1974 report that had pointed out many qualitatively similar deficiencies. In its current 1982 report, the GAO concluded that the new review *"of FDA's monitoring of prescription drugs showed that many of the problems found in 1974 still exist."*

Now in the spring of 1983, the efficiency and effectiveness of the FDA's system has again come into question.

As part of the "fallout" from the Zomax recall, the U.S. House of Representatives Subcommittee on Intergovernmental Relations held oversight hearings on April 26–27 specifically targeted at reviewing (*a*) the decision to approve the marketing of Zomax, (*b*) the ADR reports that followed its approval, and (*c*) the decision to remove it—at least temporarily—from the market. And from those specific considerations, questions and concerns gradually broadened to the more general subject of the agency's ADR reporting system in overall.

Press reports summarizing the two-day congressional hearing cryptically concluded that even FDA officials admit significant flaws still exist in the system. For example, *The Wall Street Journal* reported:

"The FDA's system for tracking reports of adverse drug reactions is significantly flawed, agency officials suggested in congressional testimony.

"One official told a House subcommittee that he had been surprised to learn from Johnson & Johnson that the company knew of nearly twice as many instances of adverse reactions (1,100) from its prescription pain reliever Zomax than the agency had known about (500 to 600)."

Our purpose here is not to point an accusing finger at FDA or anyone else. The FDA has long recognized its weakness in this area and explains that limitations of personnel and resources are the root cause of such weakness in this as well as several other areas of its responsibility. This prompts many agency observers to wonder whether some readjustment of its priorities and budgetary allocations might not significantly relieve the situation.

But, for purposes of our present consideration, let us accept the FDA's explanation at face value. Doing so suggests to us that the broad issue of postmarketing drug surveillance, that was such a dominant health care concern 3 to 5 years ago—if not *the* dominant concern—is still very much alive. It has not been resolved. It has not gone away. It has simply been pushed aside. And it has been pushed aside not only by FDA but also by other relevant groups—the drug industry, health care practitioners, their professional societies, and pertinent trade and consumerist organizations.

Although practically studied to death by various groups and organizations in the mid- to late-1970s, followed by the usual pattern of reports and recommendations, no clear-cut simple solution to the problem was identified. About the most that interested analysts seemed to be able to agree upon was that efforts should be directed at expanding and upgrading the existing system and fostering a greater awareness among practitioners for their need to participate as an on-going practice.

It is human nature that old, chronic problems spark little interest, and correspondingly little attention is usually devoted to them. In this instance, the potential major health hazards are clearly evident. Hence, they dictate that we cannot allow disinterest or "boredom" to divert us from devoting the needed efforts and resources toward improving this "significantly flawed" system.

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