PERSPECTIVES

Adverse Drug Event Monitoring at the Food and Drug Administration

Your Report Can Make a Difference

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The Food and Drug Administration (FDA) is responsible not only for approving drugs but also for monitoring their safety after they reach the market. The complete adverse event profile of a drug is not known at the time of approval because of the small sample size, short duration, and limited generalizability of pre-approval clinical trials. This report describes the FDA's postmarketing surveillance system, to which many clinicians submit reports of adverse drug events encountered while treating their patients. Despite its limitations, the spontaneous reporting system is an extremely valuable mechanism by which hazards with drugs that were not observed or recognized at the time of approval are identified. Physicians are strongly encouraged to submit reports of adverse outcomes with suspect drugs to the FDA, and their reports make a difference. The FDA is strengthening its postmarketing surveillance with access to new data sources that have the potential to further improve the identification, quantification, and subsequent management of drug risk.

KEY WORDS: **Food and Drug Administration (FDA); adverse drug events; postmarketing surveillance; MedWatch; drug withdrawals.**

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When the Food and Drug Administration (FDA) approves a new drug for marketing, its complete adverse event profile may not be known because of the limitations of pre-approval clinical trials. Typically, clinical trials for new drugs are of short duration and are conducted in populations that number from a few hundred to several thousand; therefore, the most common dose-related adverse drug reactions are usually detected in the premarketing phase. Since most trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medications suspected of interaction with the study drug, the studies' participants may not be representative of the real world where the drug is eventually used.[1] An analysis of 192 randomized drug trials found that the quality and quantity of safety reporting may sometimes be presented erratically or may be missing altogether.[2]

The FDA is responsible not only for approving drugs for marketing but also for monitoring their safety after they reach the market. This function is carried out by the FDA's Office of Drug Safety, which maintains a spontaneous reporting database called the Adverse Event Reporting System (AERS). AERS receives adverse events information from 2 principal sources: mandatory reports from pharmaceutical companies on adverse events that had been spontaneously communicated to the firms, primarily by physicians and pharmacists; and adverse event reports that physicians, pharmacists, nurses, dentists, and consumers submit directly to the FDA's MedWatch program.[3,4] Since 1969, more than 2 million adverse event reports have been submitted to the FDA. Currently, the agency receives approximately 250,000 of these reports per year. In the United States, the estimated cost of morbidity and mortality related to adverse drug reactions (ADRs) is more than $75 billion annually, and ADRs are among the top 10 leading causes of death.[5,6]

The majority of reports that are submitted to the FDA come from pharmaceutical companies. However, late or non-reporting of case reports by drug companies, or failure to report any adverse event at all, are major problems. The makers of the arthritis medication benoxaprofen (Oraflex), the antihypertensive drug ticrynafen (Selacryn), and the antidepressant drug nomifensine (Merital) have been criminally prosecuted for delay in reporting or failure to report serious adverse drug events. In recent years, the FDA has issued several warning letters to companies, primarily as a result of the late reporting of adverse drug events.

Timely reporting of adverse events is fundamental to the success of the FDA's postmarketing surveillance (PMS) program, especially in the case of newly marketed drugs. Physicians are on the frontline of FDA's PMS program, and their reports make a difference. Inadequate reporting of adverse events by physicians may delay detection of postmarketing adverse drug events.[7] There is no program of testing prior to the marketing of a drug that will find all its risks in real-world situations, and no drug is completely

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safe. The objective of this paper is to describe the FDA's PMS program and to highlight the important role of physicians and other health care professionals in this task with the hope that this will stimulate and encourage increased reporting of serious adverse events associated with drugs. It is only with the help of alert and vigilant physicians and other health care professionals that new risks of drugs are uncovered.

IDENTIFICATION OF SAFETY PROBLEMS

Spontaneous reporting systems such as AERS are the most common, effective, and relatively inexpensive methods used in pharmacovigilance to identify new or rare adverse events. Data from AERS are first scrutinized by the FDA's postmarketing safety evaluators for previously unrecognized (unlabeled) serious adverse events, which may represent potential "signals." Most helpful in this process are "good" adverse event reports that contain information such as: a complete description of the adverse outcome; baseline status of the individual; laboratory values and biopsy report, where applicable; temporal relationship with the suspect drug; information about dechallenge (event abates when drug is discontinued) and rechallenge (event recurs when drug is restarted); and information about confounding drugs or conditions. Even a single "good" adverse event report can qualify as a potential "signal" that requires further research.

When a "signal" is noted, the safety evaluators, who are specially trained clinical pharmacists, routinely try to find additional cases in AERS and medical literature or from foreign regulatory agencies. A case definition may be developed and repeatedly refined as new cases are collected. After assembling a series of cases, the safety evaluators search for any common trend, causal relationship, or pattern of events to identify potential risk factors or any other peculiarities. Usually, they look for signs such as: temporal association (the suspect drug was taken before the occurrence of adverse outcome); coherence with existing information or biological plausibility; similar effect in drugs of the same class; dose-response relationship; consistency of the association (replicability of results); and specificity of association.

One of the limitations of spontaneous reports is that, in general, they are poorly documented, and the safety evaluator may need to contact the event reporter, either directly or through the manufacturer, in order to secure follow-up information.

Another limitation of spontaneous reporting is that it captures only a small fraction of the adverse events that actually take place. The extent of under-reporting is unknown, and depends on the severity of the adverse event, among other factors. One group of researchers estimated that the FDA receives reports of less than 1% of serious adverse events, whereas another group gave this estimate as between 8% and 13%.[8,9] Since it is not possible to calculate from the available information the actual incidence of adverse events, the FDA's epidemiologists frequently estimate the reporting rate (number of case reports of adverse outcome of interest divided by estimated total number of prescriptions) of adverse events with a suspect drug, and compare it with the background rate at which the same event occurs in a population not treated by the suspect drug. A reporting rate that is higher than the background rate is an indication of a possible causal relationship between the adverse event and the drug.

CONFIRMATION OF SIGNAL

As the next step, the FDA may attempt to confirm potential signals by conducting studies in one of several large claims databases that link prescriptions with adverse outcomes. The FDA has funded extramural investigators through a system of cooperative agreement for more than a decade. These investigators, who have access to large population-based databases, are affiliated with departments of pharmacoepidemiology and/or pharmacy in universities and/or managed care organizations/HMOs. Over the years, the FDA has been able to utilize the resources of these investigators to answer a number of drug safety questions. The FDA may also query foreign regulatory agencies, mainly those in Europe, Canada, and Australia, regarding whether similar adverse events may have been reported with the suspect drug. In addition, the FDA may query the World Health Organization (WHO) Uppsala Monitoring Center database, which collects adverse drug reactions data from over 60 countries participating in the WHO International Drug Monitoring Program.[10]

EXAMPLES OF FDA REGULATORY ACTIONS STIMULATED BY ADR REPORTS

The confirmation of a "signal" may be followed by one or more FDA regulatory actions, the extent and rigor of which depend on the seriousness of the adverse events, the availability, safety, and acceptability of alternative therapy, and the outcome of previous regulatory intervention. The agency may require the drug manufacturer to inform prescribers about the identified hazard in a "Dear Health Care Professional" letter, and to add to or strengthen new or boxed warning information in the product's professional labeling. Boxed warning may be required when special problems, particularly those that may lead to death or serious injury, may be associated with a drug. If a boxed warning is required, its location is specified by the agency. The FDA may also require that the drug company enhance patient information materials such as medication guides.

Recent examples of FDA regulatory actions stimulated by ADR reports include postmarketing reports of myocarditis in association with clozapine (Clozaril), which led to strengthening of the boxed warning and warnings section of the drug's labeling; and reports of liver failure leading to transplants and/or death in association with the use of the antidepressant nefazodone (Serzone), which led to the

Table 1. Recent Safety-based Drug Withdrawals

Drug	Adverse Event	Year of Withdrawal
Terfenadine (Seldane)	Drug interactions/arrhythmias (*torsades de pointes*)	1998
Bromfenac (Duract)	Hepatotoxicity	1998
Mibefradil (Posicor)	Drug interactions	1998
Astemizole (Hismanal)	Drug interactions/arrhythmias (*torsades de pointes*)	1999
Grepafloxacin (Raxar)	Arrhythmias	1999
Troglitazone (Rezulin)	Hepatotoxicity	2000
Cisapride* (Propulsid)	Drug interactions	2000
Phenylpropanolamine†	Hemorrhagic stroke	2000
Alosetron (Lotronex)‡	Ischemic colitis	2000
Rapacuronium bromide (Raplon)	Bronchospasm	2001
Cerivastatin (Baycol)	Rhabdomyolysis	2001

* *Cisapride is available only through an investigational limited-access program.*
† *Phenylpropanolamine or PPA was an ingredient in many cough/cold and diet pills.*
‡ *In June 2002, the FDA approved restricted remarketing of alosetron.*
Detailed information on all the above drugs can be accessed by visiting the FDA's website (www.fda.gov/medwatch/safety.htm).

addition of a black box warning in the labeling. A boxed warning was added following spontaneous reports of serious cardiac arrhythmias in association with the use of levomethadyl acetate (Orlaam), a drug for opiate addiction treatment. The warnings, precautions, and adverse reactions section of labeling for the two antidiabetic drugs pioglitazone (Actos) and rosiglitazone (Avandia) were strengthened, and physicians and patients with diabetes were alerted to the possibility of fluid retention that could lead to or exacerbate congestive heart failure when either drug was used as monotherapy or in combination with insulin. The FDA issued a public health advisory concerning the systemic use of two antifungals itraconazole (Sporanox) and terbinafine (Lamisil) and the association of serious hepatic events with both drugs and possible association of serious cardiac adverse events with the administration of itraconazole.

The FDA can also restrict distribution of a drug, and on rare occasions, it may request a drug's withdrawal from the market, or the manufacturer may voluntarily withdraw the drug. The cholesterol-lowering drug cerivastatin (Baycol) was voluntarily withdrawn from the market by the drug's manufacturer following serious reports of rhabdomyolysis in association with its use. The irritable bowel syndrome drug alosetron (Lotronex) was withdrawn from the market by the company following postmarketing reports of ischemic colitis a few months after the drug was launched in the market. In June 2002, the FDA approved restricted marketing of alosetron. The diabetes drug troglitazone and the heartburn drug cisapride are recent examples of drugs that were removed from the market after repeated labeling changes and "Dear Health Care Professional" letters to clinicians did not achieve meaningful improvement in liver enzyme testing or prevention of contraindicated drug use, respectively (see Table 1 for recent examples of drugs withdrawn for reasons of safety).[11,12]

Frequently, the FDA informs the public about these actions in a press release or a public health advisory. In addition, the agency regularly disseminates new drug safety information on its website (www.fda.gov/medwatch/safety.htm), through articles in professional journals,[13–26] and at scientific forums where FDA scientists give presentations.

CONCLUSION

The FDA is strengthening its postmarketing surveillance system with new staff and resources in order to meet the challenges of the changing world of therapeutics. Ensuring the safety and effectiveness of drugs on the market, however, is a responsibility that the FDA shares with industry, all health care professionals, including physicians and pharmacists, and patients. The FDA's success in reducing drug-related adverse events depends to a large extent on the adverse event reports it receives from health care professionals, either directly or through the manufacturers. Health care practitioners are on the front line of the FDA's postmarketing program, and their reports are vital to the FDA's ability to protect consumers and patients. Physicians are strongly encouraged to submit reports of adverse outcomes with suspect drugs to the FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178), or via the MedWatch website at http://www.fda.gov/medwatch.

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