

# Adverse Drug Event Surveillance and Drug Withdrawals in the United States, 1969-2002

## *The Importance of Reporting Suspected Reactions*

Diane K. Wysowski, PhD; Lynette Swartz, MEd, MBA

**Background:** The Adverse Event Reporting System is the primary surveillance database used by the Food and Drug Administration for identifying postmarketing drug safety problems.

**Methods:** We analyzed all reports of suspected adverse drug reactions submitted to the Food and Drug Administration from the inception of the Adverse Event Reporting System database in 1969 through December 2002. We documented drug withdrawals and restricted distribution programs based on safety concerns.

**Results:** During the 33-year period from 1969 when adverse drug event reporting was initiated through 2002, about 2.3 million case reports of adverse events for the cumulative number of approximately 6000 marketed drugs were entered in the database. Most reports were for female patients. During this period, numerous drug reactions have been identified and added to the product labeling as boxed warnings, warnings, precautions, contraindications, and adverse reactions. More than 75 drugs/drug products have been removed from the market due

to safety problems. In addition, 11 drugs have special requirements for prescriptions or have restricted distribution programs. Drugs withdrawn or restricted represent a small proportion (about 1%) of marketed drugs.

**Conclusions:** The Food and Drug Administration's Adverse Event Reporting System is the primary surveillance database used for the identification of safety problems of marketed drugs. Despite the limitations of underreporting, differential reporting, and uneven quality, submitted reports often allow the identification of serious adverse events that are added to the product labeling information. In rare instances, additional regulations, up to and including market removal, have been required. We encourage physicians, pharmacists, other health care professionals, and patients to continue to report serious suspected and known adverse drug reactions to manufacturers and the Food and Drug Administration.

*Arch Intern Med.* 2005;165:1363-1369

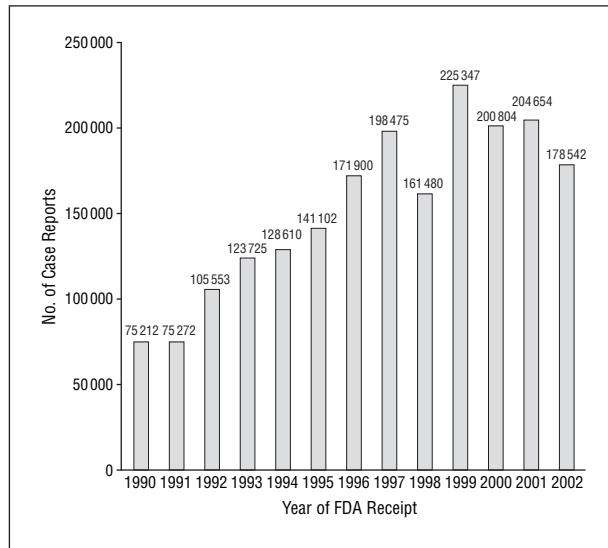
**A** PRIMARY MISSION OF THE Center for Drug Evaluation and Research of the Food and Drug Administration (FDA) is the review and approval for marketing of safe and effective drugs and certain biologic agents. Before approval, drugs are evaluated for a defined indication in clinical trials of relatively short duration in a relatively small number and in restricted categories of people. Following approval and marketing, when the drug is used in larger populations for longer durations and for unapproved indications, previously unidentified adverse drug events often occur. Some of these events have been serious and frequent enough or have altered the risk-benefit ratio enough to result in the drug's removal from the market.

A primary source of information used by the FDA for identifying postmarketing drug safety problems is surveillance of voluntarily submitted adverse drug event reports. Reports are sent by health care professionals, consumers, drug manufacturers, and others to the FDA, where they are organized in a database referred to as the Adverse Event Reporting System (AERS), previously known as the Spontaneous Reporting System. Herein, we describe adverse drug event reports submitted to this database from its inception in 1969 through December 2002 and provide information on associated regulatory actions, including drugs removed for safety reasons.

**Author Affiliations:** Office of Drug Safety, Food and Drug Administration, Rockville, Md.  
**Financial Disclosure:** None.

### METHODS

The Office of Drug Safety (formerly the Office of Post-Marketing Drug Risk Assessment) of



**Figure.** Number of case reports entered in the Adverse Event Reporting System from 1990 through 2002. FDA indicates Food and Drug Administration.

the FDA receives reports of adverse drug events primarily from physicians and pharmacists who submit them on a standardized form (referred to as the MedWatch form) indirectly through pharmaceutical companies or directly to the FDA. Health practitioners and patients may also report adverse drug events by telephone or by accessing the MedWatch Internet site. Published reports of adverse drug reactions also may be submitted.

Each report is entered into the AERS computerized database using a coding thesaurus of adverse reaction terms used for searching and retrieval purposes. Reports are entered manually; in late 1997, the system was redesigned to begin accepting a growing number of electronic reports submitted by pharmaceutical companies.

The process for identifying adverse events and for initiating regulatory action for drug safety problems is as follows: FDA safety staff (primarily pharmacists) receive AERS reports daily and review them for possible drug causality. After a sufficient number of convincing reports and/or other data (including published studies and case reports) have accumulated implicating the drug with a reaction, pharmacists and epidemiologists present the evidence in writing to the division that reviewed and approved the drug. If the reviewing division agrees that the data are compelling enough to require regulatory action (eg, a change in the product information), it notifies the manufacturer and requests the action. Disagreements between manufacturers and the FDA may be resolved through formal dispute resolution and the use of an Advisory Committee.<sup>1</sup> Title 21 of the *Code of Federal Regulations* (eg, Sections 2.5, 7.1-7.87, 314.150, and 314.151) describe regulatory actions that can be taken for the removal of a drug for safety reasons.<sup>2</sup> These include recall procedures (usually for lot specific problems), declaration of the drug as an imminent hazard (invoked only once for phenformin and lactic acidosis), and notification of a judicial hearing.<sup>3</sup> In most situations after important safety problems become evident, drugs are voluntarily withdrawn by the market authorization holder.

The AERS data are reviewed by safety staff for duplicate and follow-up reports. Follow-up to obtain additional information occasionally is conducted by manufacturers and rarely by FDA staff (because of limited resources). Technology has enabled linkage of follow-up and initial reports as case reports. For this article, case report counts were obtained, but some duplicate

and follow-up reports cannot be identified, so the numbers do not refer to individual persons. Reports are entered continuously. The data in this article refer to those accessed from June to August 2003.

Reports with serious outcomes (death, life-threatening event, hospitalization, disability, congenital malformation, and event that required medical intervention) are required to be submitted by drug manufacturers to the FDA within 15 days of receipt and are priorities for analysis. A separate serious outcome category referred to as "other" that was added in 1997 was not included in our tally of serious reports.

Previously, no more than 5 adverse events per report were entered in the AERS, but in 1997 the system was restructured to allow entry of all adverse events mentioned in the text. Because all adverse events are entered but serious events are not identified as such, relatively nonserious events may be included in lists of events with serious outcomes.

We analyzed reports by year, country, sex, age, and adverse events. We identified drugs and drug products that have been removed from the market or have restricted distribution programs because of safety reasons—many of which were found or confirmed using the AERS database.

## RESULTS

During the 33-year period from 1969 when adverse drug event reporting was initiated through 2002, about 2.3 million case reports of adverse events for marketed drugs were entered in the AERS database. Through 1997, there was a continuous increase in the annual number of reports entered. Beginning in 1998, annual changes have been inconsistent (**Figure**). Compared with 1999, the peak year for receipt and entry of reports, in 2002, reporting declined 21%. This, in part, may be because of the FDA's recent procedural change to discontinue entry of reports with nonserious outcomes for drugs approved longer than 3 years and to allow market authorization holders waivers for submission of reports with adverse events that have nonserious outcomes and that are already mentioned in the product labeling.

About 1.8 million reports (about 80%) originated from reporters in the United States. The second largest source was from unidentified countries. Assuming that these originated in this country, the proportion of US reports was 87%. The country with the second largest number was France (64 021 reports), followed by the United Kingdom (45 864 reports) and Japan (41 053 reports). No country besides the United States had more than 3% of the total number of reports. Most reports (53%) concerned female patients, 35% referred to male patients, and 12% did not specify sex. Patient age was less well reported than sex, with 30% of reports having unspecified ages. Of the reports, 5% were for patients 14 years or younger, 24% concerned those aged 15 to 44 years, 16% were for those aged 45 through 59 years, and 25% referred to those 60 years and older. Race is not a separate field on the form. For 1969 through 2002, about 60% of reports were from health care professionals, 29% were from consumers, and the remainder were from study and literature reports, company data, and other sources. Overall, 29% of reports had serious outcomes.

**Table 1** presents the most frequently reported adverse events for all reports entered in the AERS through

**Table 1. Top 20 Adverse Events Reported for Drugs From 1969 Through 2002\***

Adverse Event	No. of Reports
Drug ineffective	151 431
Dermatitis NOS	122 171
Headache	80 308
Nausea	76 900
Pruritus NOS	74 869
Pyrexia NOS	74 817
Dyspnea NOS	74 205
Dizziness (excluding vertigo)	72 995
Vomiting NOS	69 818
Urticaria NOS	61 965
Asthenia	59 607
Pain NOS	57 635
Abdominal pain NOS	56 400
Condition aggravated	55 659
Diarrhea NOS	53 959
Chest pain	44 077
Hypotension NOS	41 931
Alopecia	39 062
Sedation	36 830
Convulsions NOS	35 813

Abbreviation: NOS, not otherwise specified.

\*Based on case counts in the Food and Drug Administration's Adverse Event Reporting System database as of June 23, 2003. Includes reports from all countries.

**Table 2. Top 20 Adverse Events With Serious Outcomes Reported for Drugs From 1969 Through 2002\***

Adverse Event	No. of Reports
Pyrexia	41 529
Dyspnea NOS	35 717
Vomiting NOS	28 928
Hypotension NOS	24 977
Condition aggravated	23 156
Death NOS	20 991
Asthenia	20 268
Pneumonia NOS	19 146
Convulsions NOS	19 043
Cardiac arrest	18 295
Chest pain	17 847
Nausea	17 841
Thrombocytopenia	17 820
Abdominal pain NOS	16 803
Myocardial infarction	16 742
Dermatitis NOS	15 778
Dizziness (excluding vertigo)	15 505
Diarrhea NOS	15 454
Sepsis NOS	15 133
Confusion	14 764

Abbreviation: NOS, not otherwise specified.

\*Based on case counts in the Food and Drug Administration's Adverse Event Reporting System database as of June 23, 2003. Includes reports from all countries.

2002. The event with the highest count was drug ineffective, with 151 431 reports. This was followed by dermatitis, headache, nausea, pruritus, pyrexia, dyspnea, dizziness (exclusive of vertigo), vomiting, and urticaria (several of which are indicative of hypersensitivity/allergic reactions). The leading events associated with serious outcomes (**Table 2**) included pyrexia, with 41 529 reports, followed by dyspnea, vomiting, hypotension, condition aggravated, death, asthenia, pneumonia, convulsions, cardiac arrest, and chest pain.

Since its inception in 1969, the AERS database has provided evidence that certain approved drugs/drug products posed serious safety problems. Some drugs have been removed from the market, based in whole or in part, on adverse event reports. **Table 3** provides a list of known drugs/drug products removed from the market, dating from 1964, because of safety reasons.<sup>4-7</sup> For many of these products, safety concerns were identified from spontaneous reports or in clinical trials with verification from spontaneous reports, although good historical data are lacking. **Table 4** provides a list of drugs/drug products that were removed from 1978 through mid 2003.<sup>4-7</sup> Considering that, as of fall 2003, an estimated 6000 trade name drugs were in the US marketplace (Pat Muller, RPh, National Drug Data File [NDDF] Plus, First DataBank, written communication, 2003), the proportion of drugs withdrawn from marketing for safety reasons has been small. In the 1960s, there were only 532 suspect (for causality) trade name drugs entered in the AERS when 8 drugs/drug products were removed from distribution. Comparable numbers were 36 drugs/drug products removed of 1655 entered in the AERS during the 1970s, 13 of 2357 in the 1980s,

14 of 4129 in the 1990s, and 6 of 3952 entered thus far in the 2000s (counts from both Tables 3 and 4).

In addition to those removed, 11 drugs have special requirements for prescription or have restricted distribution programs (**Table 5**). These include clozapine, isotretinoin, fentanyl, trovafloxacin, thalidomide, bosentan, mifepristone, alosetron, sodium oxybate, and dofetilide. Three teratogenic drugs (isotretinoin, acitretin, and thalidomide) have formal pregnancy prevention risk management programs.<sup>10</sup>

Besides providing evidence prompting removal and restricted distribution programs of certain drugs, AERS reports also have provided information leading to the addition of boxed warnings, warnings, precautions, contraindications, and adverse reactions to the product information labeling<sup>11</sup> and the provision of information to patient package inserts and patient medication guides.<sup>12</sup>

#### COMMENT

Since 1969, a spontaneous reporting system of suspected adverse drug reactions has provided the FDA with drug surveillance information and has supported regulatory decisions about the safety of the approximately 6000 marketed drugs. Because more than 10 000 separate adverse event terms have been used in connection with these drugs, the AERS database is a rich source of drug safety information.

Although the AERS is a valuable resource, an accumulation of well-documented reports does not by itself indicate a causal relationship between a drug and an adverse event. Rather, the spontaneous reports that make

**Table 3. Drugs/Drug Products Removed From Marketing or Distribution for Safety Reasons in the United States From 1964 to 1993\***

Year	Drug (Trade Name)	Reason
1964	Butamben, parenteral (Efocaine)	Severe tissue slough, transverse myelitis
	Casein, iodinated	Thyrototoxic adverse effects
1965	Methopholine (Versidyne tablets)	Corneal opacities in dogs
1966	Sulfadimethoxine (Madricidin tablets)	Stevens-Johnson syndrome
	Aminoglutethimide†	Endocrine disorders <sup>4</sup>
1967	Bithionol	Serious skin disorders
	Cobalt salts, with certain exceptions	Liver/heart damage, claudication
1969	Pipamazine (Mornidine tablets and injection)	Hepatic lesions
1970	Sulfathiazole (Tresamide tablets)	Renal complications, rash, fever, blood dyscrasias, liver damage
	Dihydrostreptomycin sulfate	Ototoxicity
	Mepazine (Pacatal tablets and injection)	Granulocytopenia, granulocytosis, paralytic ileus, seizures, hypotension, jaundice, urinary retention
	Aminopyrine	Bone marrow suppression <sup>4</sup>
1972	Gonadotropin, chorionic—animal origin	Allergic reactions
	Oxyphenisatin acetate (Prulet)	Hepatitis, jaundice
	Carbetapentane citrate oral gel (Candette Cough Jel)	Inexact measurement of gel
	Chlormadinone acetate (Estalor-21, C-Quens)	Mammary tumors in dogs
1973	Adenosine phosphate (Adeno injection, Adco injection)	Not safe for intended use as vasodilator, anti-inflammatory
	Methamphetamine hydrochloride (Methedrine injection, Drinalfa injection)	Abuse, dependence
	Oxyphenisatin (Lavema Compound Solution, Lavema Enema Powder)	Hepatitis, jaundice
	Clioquinol oral	Neurotoxicity <sup>4</sup>
1974	Vinyl chloride aerosol	Acute CNS toxicity
	Nialamide	Liver damage, drug interactions <sup>4</sup>
1974, 1975	Nitrofurazone nasal drops, otic drops, vaginal suppository	Mammary neoplasia in rats
1975	Diethylstilbestrol, oral and parenteral, with $\geq 25$ mg per unit dose	Adenocarcinoma of vagina in daughters after use in early pregnancy
	Dibromsalan	Serious skin disorders
	Metabromsalan	Serious skin disorders
	Tribromsalan	Serious skin disorders
	3,3,4,5-Tetrachlorosalicylanilide	Serious skin disorders
1976	Chloroform	Carcinogenic in animals
1977	Azaribine (Triazure tablets)	Thromboembolic events
	Dipyron (Dimethone tablets and injection, Protemp oral liquid)	Agranulocytosis
	Diamthazole dihydrochloride (Asterol ointment, powder, tincture)	Neurotoxicity
	Reserpine, $>1$ mg (Reserpoid tablets)	More frequent, more severe adverse effects
	Trichloroethane aerosol	Potential CV toxicity, deaths from misuse, abuse
	Urethane (Profenil injection)	Carcinogenic
	Zirconium aerosol	Human skin granulomas, toxicity in test animals
1977, 1992	Potassium chloride—concentrated solid oral dosage forms with $\geq 100$ mg of potassium per dosage unit with certain exceptions	Small-bowel lesions
1978	Adrenal cortex	Undertreatment of serious conditions
	Gelatin, intravenous	Increased blood viscosity, reduced blood clotting, prolonged bleeding time
	Tetracycline for oral pediatric use, with $>25$ mg/mL	Inhibition of bone growth, permanent staining of teeth, enamel hypoplasia
	Povidone (polyvinylpyrrolidone), intravenous	Accumulation, storage disease, interferes with blood coagulation, blood-typing, crossmatching
1979	Sparteine sulfate (Spartocin injection, Tocosamine sterile solution)	Tetanic uterine contractions, obstetrical complications
	Methapyrilene	Potent carcinogen
1980	Potassium arsenite (Fowler solution)	Toxicity, potent carcinogen
	Sweet spirits of nitre	Infant methemoglobinemia
1982	Camphorated oil	Infant, child poisoning
1983	Phenacetin (APC tablets)	Kidney damage, hemolytic anemia, methemoglobinemia from abuse
1984	Chlorhexidine gluconate topical tincture (Hibitane)	Chemical, thermal burns
1985	Oxyphenbutazone (Tandearil)	Blood dyscrasias <sup>5</sup>
1989	Neomycin sulfate, parenteral	Toxicity for irrigation of wounds, other safer antibiotics
1993	Glycerol, iodinated (Iodur Elixir)	Carcinogenic potential

Abbreviations: APC, aspirin, phenacetin, and caffeine; CNS, central nervous system; CV, cardiovascular.

\*Data are from published lists.<sup>4-7</sup>

†Reintroduced for treatment of hormone-dependent malignant tumors.<sup>4</sup>

**Table 4. Drugs Removed From Marketing or Distribution for Safety Reasons, With Identification/Evidence From Spontaneous or Case Reports, United States, From 1978 to Mid-2003\***

Year	Drug (Trade Name)	Indication	Reason
1978	Phenformin (DBI)	Diabetes mellitus	Lactic acidosis
1980	Ticrynafen (Selacryn)	Uricosuric, diuretic	Hepatotoxicity
1982	Benoxaprofen (Oraflex)	Nonsteroidal anti-inflammatory	Hepatotoxicity
1983	Zomepirac sodium (Zomax)	Nonsteroidal anti-inflammatory	Anaphylaxis
1985	Pituitary growth hormone (IND)	Growth hormone deficiency	Creutzfeldt-Jakob disease
1986	Nomifensine (Merital)	Antidepressant	Hemolytic anemia
1987	Suprofen (Suprol)	Nonsteroidal anti-inflammatory	Flank pain syndrome
1991	Guar gum (Calban)	Over-the-counter diet aid	Esophageal obstruction
	Encainide (Encaid)	Antiarrhythmic	Excess mortality†
1992 (Approved 1992)	Temafloxacin (Omniflox)	Antibiotic	Hemolytic anemia (often accompanied by renal or hepatic dysfunction and/or coagulopathy)
1993 (Approved 1992)	Flosequinan (Manoplax)	Antiarrhythmic	Excess mortality
1997	Phenolphthalein (Ex-Lax)	Over-the-counter laxative	Carcinogenicity‡
1997 (Approved 1973)	Fenfluramine (Pondimin)	Diet aid for obesity	Cardiac valvulopathy
1997 (Approved 1996)	Dexfenfluramine hydrochloride (Redux)	Diet aid for obesity	Cardiac valvulopathy
1997 (Approved 1985)	Terfenadine (Seldane)	Antihistamine	Drug interactions/ventricular arrhythmias
1998 (Approved 1998)	Mibefradil (Posicor)	Antihypertensive	Drug interactions/cardiac events
1998 (Approved 1997)	Bromfenac (Duract)	Nonsteroidal anti-inflammatory	Hepatotoxicity
1999 (Approved 1988)	Astemizole (Hismanal)	Antihistamine	Drug interactions/ventricular arrhythmias
1999 (Approved 1997)	Grepafloxacin hydrochloride (Raxar)	Antibiotic	Ventricular arrhythmias
2000 (Approved 1997)	Troglitazone (Rezulin)	Diabetes mellitus	Hepatotoxicity
2000 (Approved 1993)	Cisapride (Propulsid)	Nocturnal heartburn	Drug interactions/ventricular arrhythmias
2000 (Approved 2000)	Alosetron hydrochloride (Lotronex)§	Irritable bowel syndrome	Ischemic colitis and complications of constipation
2000	Phenylpropanolamine ingredient products (eg, Dexatrim)	Over-the-counter diet aid, cough remedy, and cold remedy	Hemorrhagic stroke
2001 (Approved 1999)	Rapacuronium bromide (Raplon)	Anesthesia	Bronchospasm
2001 (Approved 1997)	Cerivastatin sodium (Baycol)	Hypercholesterolemia	Rhabdomyolysis

Abbreviation: IND, Investigational New Drug.

\*Drugs with individual indications withdrawn for reasons of safety are not included (eg, bromocriptine mesylate [Parlodel] for suppression of physiological lactation in 1994). Table does not include drugs withdrawn for other reasons (eg, market decline and altered benefit to risk [cardiac arrhythmia] for Orlaam<sup>8</sup> and limitations in component supplies for Norplant,<sup>9</sup> etc). Data are from published lists.<sup>6,7</sup> L-Tryptophan, an over-the-counter nutritional supplement and sleep aid (not classified as a drug), was removed from the market in 1990 because of its association with eosinophilia myalgia syndrome. Ephedra, an over-the-counter nutritional supplement and diet aid (not classified as a drug), was removed from the market in 2004 because of its association with heart attack, stroke, and sudden death.

†Determined from clinical trial, not spontaneous reports.

‡Based on animal studies.

§Based on clinical trial data and spontaneous reports; reintroduced to the market in 2002.

up the AERS database are often considered as early warning signals, hypothesis generating, or preliminary evidence with causality assessments often requiring additional supporting data from clinical trials and/or published studies. However, in certain circumstances, analyses of spontaneous reports can lead to an assessment that a drug and a usually relatively rare outcome are causally related. Criteria for such circumstances often include<sup>13</sup> a temporal relationship between the drug and a rare (often drug-related) outcome, occurrences of positive dechallenge, occurrences of positive rechallenge, the lack of confounders or other explanations for the outcome, biological plausibility, a dose-response relationship, a consistency between US reports and those from other countries, and consistency with, or extension of, clinical trial data. In some situations, using numbers of adverse events and drug exposure data, it is possible to determine whether the rate of the reported adverse event approaches or exceeds the

background rate for the outcome in a comparable age and sex group of the general population.<sup>14</sup> Also, using AERS reports, it is possible to determine if drugs in the same class, but not in other classes, report a particular adverse event, and how the number of reports for the event compares with the numbers associated with other drugs in the AERS database. Data mining of AERS reports also may assist in the identification of adverse event signals.<sup>15</sup>

Despite these possibilities for using the AERS data, evaluation of reports is often limited by underreporting, possible differential product reporting, and an uneven quality of submitted reports. However, these limitations have not resulted in disuse of the data. While investigators have reported that active surveillance of a particular adverse drug event, eg, thrombotic thrombocytopenic purpura with clopidogrel,<sup>16</sup> provided more complete, timely, and certain diagnoses than voluntary reporting

**Table 5. Drugs With Special Requirements for Prescribing or With Restricted Distribution Programs Because of Safety Problems, United States, From 1990 to 2002**

Drug (Trade Name)	Date Approved	Indication	Safety Problem	Date Program Initiated
Clozapine (Clozaril)	1990	Schizophrenia	Agranulocytosis	At approval in 1990, revised 1992
Isotretinoin (Accutane)	1982	Severe recalcitrant cystic acne	Teratogenicity	Postmarketing in 1989, revised 2002, 2004
Fentanyl (Fentanyl Oralet)	1993	Anesthesia, pain	Abuse, diversion	At approval in 1993
Fentanyl (Actiq Oral Transmucosal)	1999	Cancer pain with opioid tolerance	Child safety, abuse, diversion, patient selection	At approval in 1999
Trovafloxacin (Trovan)	1997	Serious infection	Hepatotoxicity	Postmarketing in 1998
Dofetilide (Tikosyn)	1999	Atrial fibrillation	Torsades de pointes	At approval in 1999, revised 2002
Bosentan (Tracleer)	2001	Pulmonary arterial hypertension	Hepatotoxicity, teratogenicity	At approval in 2001
Thalidomide (Thalomid)	1998	Erythema nodosum leprosum	Teratogenicity	At approval in 1998, revised 2001
Mifepristone (Mifeprex)	2000	Pregnancy termination	Patient selection and follow-up, drug security	At approval in 2000
Alosetron (Lotronex)	2002	Irritable bowel syndrome	Patient selection, ischemic colitis	Postmarketing in 2002
Sodium oxybate (Xyrem)	2002	Cataplexy in narcolepsy	Abuse, diversion	At approval in 2002

to the FDA, active surveillance probably would not have been undertaken with clopidogrel had not thrombotic thrombocytopenic purpura been identified previously by spontaneous reporting to be associated with ticlopidine,<sup>17,18</sup> a drug in the same class as clopidogrel. Furthermore, active surveillance of the many drugs and potential adverse reactions by the number and composition of FDA staff is not feasible. However, FDA epidemiologists have sometimes used an extramural cooperative agreement research program<sup>19-21</sup> or have participated in studies that have used other funding mechanisms<sup>22</sup> to conduct additional studies of selected adverse drug reactions.

Following risk assessment of a drug's safety problems using the AERS and other data, strategies to minimize the risk may be enacted. These include dose changes, product labeling changes (a continuum from adverse reactions to boxed warnings), issuance of informational health care professional letters, publication of AERS data in the medical literature,<sup>17,23-44</sup> release of FDA Talk Papers and public health advisories for press reports, inclusion of patient package inserts and medication guides with drug dispensing, written informed patient consent before prescription, restricted drug distribution, and drug removal. In the case of one drug's removal from marketing, the chronology and timing of regulatory actions in relation to the identification of the adverse event have been described in detail.<sup>23</sup> Although the timing of new boxed warnings was the focus of a recent study<sup>45</sup> and editorial,<sup>46</sup> documenting the timing of regulatory actions for the drugs removed was not the focus of this article.

Data in this report indicate that a small proportion of marketed drugs have been removed for safety reasons. Besides removal and disuse of drugs because of market competition, the FDA also relies on risk management strategies to achieve postmarketing drug safety standards. Indeed, effective science-based risk management was announced in 2003 as a major initiative of the agency<sup>47</sup>; however, risk management plans will require evaluation to determine their effectiveness in reducing drug risks.

The continuation of the receipt of adverse drug event reports is critical to the drug safety mission of the FDA.

Because the AERS data are an important source for detecting postmarketing drug safety problems, we encourage physicians, pharmacists, other health care professionals, and patients to submit reports of suspected (and known) adverse drug reactions to the drug manufacturer or the FDA. They may be reported to the FDA by completing and submitting (by mail or facsimile) the MedWatch form that is the last page of the *Physicians' Desk Reference*, by calling (telephone number: 1-800-FDA-1088), or by accessing the MedWatch Internet site (<http://www.fda.gov/medwatch>).

In September 2004, Merck & Co, Inc, voluntarily withdrew rofecoxib (Vioxx) from the global market because of an increased risk of cardiovascular events. Two months later, the FDA announced that manufacturers of isotretinoin will obtain registration of prescribers of isotretinoin, dispensing pharmacies, and patients who are prescribed the drug.<sup>48</sup> The agency also announced the requirement of documentation of a negative pregnancy test result before isotretinoin is given to women capable of becoming pregnant. In April 2005, valdecoxib (Bextra) was withdrawn from the market because of serious dermatological conditions and an unfavorable risk vs benefit profile.

In 1994, the FDA established that any over-the-counter drug products (eg, quinine sulfate) for the treatment and/or prevention of nocturnal leg cramps is not generally recognized as safe and effective and is misbranded.<sup>49</sup> 1998, the FDA established that over-the-counter drug products containing quinine for the treatment and/or prevention of malaria are not generally recognized as safe and are misbranded.<sup>50</sup>

**Accepted for Publication:** June 2, 2004.

**Correspondence:** Diane K. Wysowski, PhD, Division of Drug Risk Evaluation, HFD-430, Food and Drug Administration, 5600 Fishers Ln, Parklawn Building, Room 15B-08, Rockville, MD 20857.

**Disclaimer:** The views expressed herein are those of the authors and do not necessarily represent the official position of the FDA.

## REFERENCES

1. Food and Drug Administration, CDER and CBER. Guidance for industry: formal dispute resolution: appeals above the division level. Available at: <http://www.fda.gov/cber/gdlns/dispute.pdf>. Accessed May 7, 2004.
2. 21 CFR §2.5, §7.1-§7.87, §314.150, and §314.151.
3. Food and Drug Administration. Sandoz Pharmaceuticals Corp: bromocriptine mesylate (Parlodel) for the prevention of physiological lactation: opportunity for a hearing on a proposal to withdraw approval of the indication. *Fed Regist*. 1994; 59:43347-43352.
4. Bakke OM, Wardell WM, Lasagna L. Drug discontinuations in the United Kingdom and the United States, 1964 to 1983: issues of safety. *Clin Pharmacol Ther*. 1984;35:559-567.
5. Fung M, Thornton A, Mybeck K, Wu JH, Hornbuckle K, Muniz E. Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets: 1960 to 1999. *Drug Inf J*. 2001;35:293-317.
6. List of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness—FDA: proposed rule. *Fed Regist*. 1998;63: 54082-54089.
7. Additions to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness—FDA: proposed rules. *Fed Regist*. 2000;65:256-257.
8. US Food and Drug Administration. Drug shortage: drug to be discontinued: letter from Roxane. Available at: <http://www.fda.gov/cder/drug/shortages/orlaam.htm>. Accessed October 15, 2004.
9. US Food and Drug Administration. FDA Talk Paper: update on advisory for Norplant contraceptive kits. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01161.html>. Accessed October 15, 2004.
10. Uhl K, Kennedy DL, Kweder SL. Risk management strategies in the *Physicians' Desk Reference* product labels for pregnancy category X drugs. *Drug Saf*. 2002; 25:885-892.
11. US Food and Drug Administration. Safety-related drug labeling changes. Available at: <http://www.fda.gov/medwatch/safety.htm>. Accessed May 6, 2004.
12. US Food and Drug Administration. Patient labeling and risk communication. Available at: <http://www.fda.gov/cder/offices/ODS/labeling.htm>. Accessed May 10, 2004.
13. Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. *Clin Pharmacol Ther*. 1995; 58:692-698.
14. Wysowski DK, Farinas E, Swartz L. Comparison of reported and expected deaths in sildenafil (Viagra) users. *Am J Cardiol*. 2002;89:1331-1334.
15. Szarfman A, Machado S, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf*. 2002;25:381-392.
16. Zakarija A, Bandarenko N, Pandey DK, et al. Clopidogrel-associated TTP: an update of pharmacovigilance efforts conducted by independent researchers, pharmaceutical suppliers, and the Food and Drug Administration. *Stroke*. 2004; 35:533-538.
17. Wysowski DK, Bacsanyi J. Blood dyscrasias and hematologic reactions in ticlopidine users [letter]. *JAMA*. 1996;276:952.
18. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, Yarnold PR, Kwaan HC, Green D. Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med*. 1998;128:541-544.
19. Beck P, Wysowski DK, Downey W, Butler-Jones D. Statin use and the risk of breast cancer. *J Clin Epidemiol*. 2003;56:280-285.
20. Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care*. 1999;22:925-927.
21. Graham DJ, Drinkard CR, Shatin D. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol*. 2003;98:175-179.
22. Mills JL, Schonberger LB, Wysowski DK, et al. Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients. *J Pediatr*. 2004; 144:430-436.
23. Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. *Am J Gastroenterol*. 2001;96:1698-1703.
24. Wysowski DK, Talarico L, Bacsanyi J, Botstein P. Spinal and epidural hematoma and low-molecular-weight heparin [letter]. *N Engl J Med*. 1998;338:1774-1775.
25. Green L, Wysowski DK, Fourcroy JL. Gynecomastia and breast cancer during finasteride therapy [letter]. *N Engl J Med*. 1996;335:823.
26. Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. *J Urol*. 1996;155:209-212.
27. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA*. 1990;264:71-75.
28. Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol*. 1995;85:538-542.
29. Malozowski S, Tanner LA, Wysowski DK, Fleming GA, Stadel BV. Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. *J Pediatr*. 1995;126:996-999.
30. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: review of 95 cases. *Clin Infect Dis*. 1994;18:946-950.
31. Graham DJ, Green L. Further cases of valvular heart disease associated with fenfluramine-phentermine [letter]. *N Engl J Med*. 1997;337:635.
32. Rosa FW, Bosco LA, Graham CF, Milstien JB, Dreis M, Creamer J. Neonatal anuria with maternal angiotensin-converting enzyme inhibition. *Obstet Gynecol*. 1989; 74:371-374.
33. Arrowsmith JB, Creamer JI, Bosco L. Severe dermatologic reactions reported after treatment with tocainide. *Ann Intern Med*. 1987;107:693-696.
34. Rossi AC, Bosco L, Faich GA, Tanner A, Temple R. The importance of adverse reaction reporting by physicians: suprofen and flank pain syndrome. *JAMA*. 1988; 259:1203-1204.
35. Wysowski DK, Barash D. Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's Spontaneous Reporting System. *Arch Intern Med*. 1991;151:2003-2008.
36. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis [letter]. *N Engl J Med*. 2002;346:539-540.
37. Ahmad SR, Kortepeter C, Brinker A, Chen M, Beitz J. Renal failure associated with the use of celecoxib and rofecoxib. *Drug Saf*. 2002;25:537-544.
38. Kahn LH, Alderfer RJ, Graham DJ. Seizures reported with tramadol [letter]. *JAMA*. 1997;278:1661.
39. Faich GA, Moseley RH. Troglitazone (Rezulin) and hepatic injury. *Pharmacoepidemiol Drug Saf*. 2001;10:537-547.
40. Zitelli BJ, Alexander J, Taylor S, et al. Fatal hepatic necrosis due to pyrimethamine-sulfadoxine (Fansidar). *Ann Intern Med*. 1987;106:393-395.
41. La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States [letter]. *N Engl J Med*. 2001;345: 224-225.
42. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy*. 2002;22:841-852.
43. Wysowski DK, Honig SF, Beitz J. Uterine sarcoma associated with tamoxifen use [letter]. *N Engl J Med*. 2002;346:1832-1833.
44. Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol*. 2001;45:515-519.
45. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA*. 2002;287:2215-2220.
46. Temple RJ, Himmel MH. Safety of newly approved drugs: implications for prescribing [comment]. *JAMA*. 2002;287:2273-2275.
47. US Food and Drug Administration. Risk management. Available at: <http://www.fda.gov/oc/mcclellan/riskmngt.html>. Accessed May 3, 2004.
48. US Food and Drug Administration. FDA Talk Paper: November 23, 2004: FDA announces enhancement to isotretinoin risk management program. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01328.html>. Accessed November 23, 2004.
49. US Food and Drug Administration. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use: FDA: final rule. *Fed Regist*. 1994;59:43234-43252.
50. US Food and Drug Administration. Drug products containing quinine for the treatment and/or prevention of malaria for over-the-counter human use: FDA: final rule. *Fed Regist*. 1998;63:13526-13529.