

How the FDA Manages Drug Safety With Black Box Warnings, Use Restrictions, and Drug Removal, With Attention to Gastrointestinal Medications

Eli D. Ehrenpreis, MD¹, Arthur A. Ciociola, PhD², Prasad M. Kulkarni, MD, FACP³ and the FDA-Related Matters Committee of the American College of Gastroenterology

Am J Gastroenterol 2012;107:501–504; doi:10.1038/ajg.2011.449

Introduction

Physicians play a key role in helping the Food and Drug Administration (FDA) monitor the safety of medical products. Physicians follow the principle of Hippocrates, *primum non nocere* (“first, do no harm”). Some adverse drug reactions (ADRs) are expected due to known mechanisms of action. Others may be idiosyncratic or not previously identified and therefore may not be preventable. The FDA’s post-approval safety surveillance activities are an attempt to control these unexpected ADRs.

Background

The FDA is responsible for assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, foods, cosmetics, and radiation-emitting products (1–5). In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act after elixir of sulfanilamide (containing ethylene glycol) caused 107 deaths (5–8). The act required companies to prove a product’s safety (2,9,10). Phocomelia and other birth defects were observed following maternal use of thalidomide, prompting passage of the Kefauver–Harris Amendment in 1962. This required pharmaceutical manufacturers to report all ADRs directly to the FDA (11,12). In 2007, following a series of highly publicized drug withdrawals,

the FDA developed additional activities to enhance medical product safety (4).

The FDA evaluates all medical products before and after approval. During product development, the manufacturer performs *in vitro*, animal, and human studies. Pre-market testing takes place in a sequential fashion. Typically, testing begins with normal volunteers and then proceeds to studies to define the lowest effective dose, then to define patient populations with the optimal risk–benefit profile. However, because the total number of subjects evaluated is relatively small (<10,000), rare ADRs may not be detected before approval. The number of patients with comorbid conditions for whom safety data are collected is usually insufficient to allow for a robust risk evaluation. As a result, safety information collected in the postmarketing period is of considerable importance (13). The FDA launched the MedWatch Safety Information and Adverse Event Reporting System (AERS) in 1993 to stimulate voluntary reporting of ADRs by health-care professionals and patients.

How the FDA manages the safety of a drug

If the FDA identifies a previously unrecognized safety issue, a variety of tools are available to keep effective drugs and devices on the market while reducing risk of harm. The FDA may request further clinical stud-

ies to define and clarify adverse events. A common strategy involves requiring manufacturers to change drug labeling, also known as “prescribing information” or the “package insert.” A black box warning on a drug—the most serious type of labeling change—is designed to call attention to serious or life-threatening risk. While the FDA is considering labeling changes for a drug, it may release an Early Communication About an Ongoing Safety Review. After the review is completed, the FDA may issue a Public Health Advisory providing updated drug safety information. The FDA may also require the drug manufacturer to send a “Dear Healthcare Professional” letter outlining safety issues with advice for corrective action. A medication guide, an instruction sheet provided to the patient by the pharmacist, may be used. If these educational strategies are inadequate, additional management tools are required. These Risk Evaluation and Minimization Strategies are designed to ensure that the benefits of the product outweigh patient risk (4). They may also limit who prescribes or dispenses drugs and require physician training, laboratory testing, or registration and tracking of patients receiving the drug.

At times, further restriction or removal of a product from the market will be mandated. However, if it is determined that a drug is longer safe to remain on the mar-

¹Gastroenterology and Endoscopy, Highland Park Hospital, NorthShore University Health System, Chicago, Illinois, USA; ²Pharmaceutical Regulatory Strategy, Process, and Policy, Bausch+Lomb, Madison, New Jersey, USA; ³University of South Florida Physician’s Group, Tampa, Florida, USA. **Correspondence:** Eli D. Ehrenpreis, MD, Highland Park Hospital, NorthShore University HealthSystem, 777 Park Avenue, West Highland Park, Illinois 60035, USA. E-mail: ehrenpreis@ghpharm.net

ket, the FDA will request that the product is withdrawn. The FDA has the legal authority to immediately withdraw authorization to market a drug in the United States. In extreme situations, products may be seized to prohibit further sales. Withdrawal of a drug is communicated to the public by the manufacturer using normal media channels. The Recalls, Market Withdrawals, and Safety Alerts website (<http://www.fda.gov/Safety/Recalls/default.htm>) also gives information about withdrawn drug products. The FDA also provides MedWatch Safety Alerts and Drug Safety Podcasts and publishes a Drug Safety Newsletter. Prescribing information is available on DailyMed of the National Library of Medicine (<http://dailymed.nlm.nih.gov/dailymed/about.cfm>).

These regulatory actions are based on the evaluation of postmarketing ADRs. Data are obtained from a number of sources, including the mandatory safety reporting from the manufacturer, the AERS, published literature, and clinical and non-clinical studies. Unfortunately, fewer than 10% of all adverse safety events with medical products are reported to the FDA (13). The AERS system has also been publicly criticized for taking years to understand the risk profile of a drug and delaying removal of products from the market. In an effort to improve the postmarketing surveillance, the FDA has mandated that drug advertisements encourage patients to report ADRs. In addition, the FDA has now made the reporting form simpler and more accessible to patients and health-care providers. The FDA also initiated development of the Sentinel System in 2008, a nationwide electronic system for postmarketing tracking of drugs, biologics, and medical devices. The Sentinel System will enable the FDA to query a diverse group of health-care databases, including electronic health record systems, insurance claims databases, and medical registries. Currently, the FDA is evaluating a Mini-Sentinel program that took two years to develop and includes 17 US databases encompassing records for nearly 100,000,000 patients. The results from the Mini-Sentinel will guide the FDA in designing the final Sentinel System to improve the speed of ADR reporting. **Table 1** shows medica-

tions for gastrointestinal conditions that have undergone safety alerts.

Metoclopramide

Metoclopramide is a dopamine D₂ receptor antagonist in the chemoreceptor trigger zone as well as a mixed 5-HT₃ receptor antagonist/5-HT₄ receptor agonist and cholinomimetic. Metoclopramide increases antral contractions and small-bowel peristalsis and is a treatment for nausea and vomiting. It has also been used as a prokinetic agent. Although a variety of ADRs are associated with metoclopramide, the development of tardive dyskinesia (TD) prompted an FDA black box warning in February 2009 (14). Chronic treatment with metoclopramide can cause TD, characterized by involuntary movements of the extremities, lips, tongue, and face and eyes. TD is associated with centrally acting dopamine blockers, including phenothiazines (e.g., thiorazine and prochlorperazine). Development of TD is related to the duration of metoclopramide use and its cumulative dose. TD has no known treatment and is often irreversible. The elderly, especially women, are at highest risk. The black box warning states that prolonged treatment with metoclopramide (longer than 12 weeks) should be avoided in all but rare cases in which the therapeutic benefit outweighs the risks of developing TD.

Alosetron

Alosetron is an antagonist of serotonergic 5-HT₃ receptors of the enteric nervous system. Alosetron diminishes gastrointestinal motility, decreases noxious sensations, slows colonic motility, and enhances colonic water reabsorption. It was approved as Lotronex in February 2000 for women with diarrhea-predominant irritable bowel syndrome (IBS). In November 2000, alosetron was withdrawn from the market after reports of ischemic colitis and severe constipation resulting in hospitalization, surgery, and death (15,16). It was reintroduced in June 2002 under the approval of a supplemental new drug application (sNDA) with restricted marketing for women with severe diarrhea-predominant IBS. The sNDA includes a risk management program (17).

Tegaserod

Tegaserod is a 5-HT₄ receptor partial agonist manufactured by Novartis under the name Zelnorm. Activated 5-HT₄ receptors in the gastrointestinal tract stimulate intestinal peristalsis and secretion and inhibit visceral sensitivity. Tegaserod was approved for the management of abdominal discomfort, bloating and constipation associated with IBS (July 2002), and chronic idiopathic constipation (August 2004). In March 2007, the FDA suspended marketing and sales of tegaserod because a safety analysis found increased myocardial infarction, stroke (cerebrovascular accident), and unstable angina in patients treated with tegaserod compared with placebo. Subsequent observational studies did not concur (18). In July 2007, the FDA permitted the restricted use of tegaserod under a treatment-investigational new drug (T-IND) protocol for IBS with constipation and chronic idiopathic constipation in women younger than 55. Novartis subsequently abandoned this T-IND. Zelnorm may be available in emergency situations that are immediately life-threatening or that qualify for hospitalization. Physicians with patients who may qualify for emergency treatment with Zelnorm may contact the FDA's Division of Drug Information at druginfo@fda.hhs.gov.

Cisapride

Cisapride, a serotonin-4 (5-HT₄) receptor agonist (and partial 5-HT₃ antagonist), promotes gastric motility by enhancing release of acetylcholine at the myenteric plexus. Cisapride (marketed as Propulsid) was used between 1993 and 1999 for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. It was prescribed off-label as a prokinetic agent for gastroparesis and other motility disorders. QT prolongation and serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsade de pointes were reported with cisapride use.

Depletion of serum electrolytes further increases cardiac risk (19). Combined use of cisapride with a number of drugs, including those causing QT prolongation (tricyclics, certain antipsychotic agents) and CYP-4503A4 inhibitors (fluconazole,

Table 1. Prescribed gastrointestinal drugs, including those that have undergone status changes by the US Food and Drug Administration

Name	Black box warning	Medication guide
Adalimumab	Yes	Yes
Alosetron	Yes	Yes
Atropine	No	No
Atropine/diphenoxylate	No	No
Azathioprine	Yes	No
Balsalazide	No	No
Calcium acetate	No	No
Certolizumab	Yes	Yes
Cholestyramine	No	No
Cimetidine	No	No
Cisapride	Not applicable (discontinued)	No
Cyclosporine	Yes	Yes
Dicyclomine	No	No
Dronabinol	No	No
Famotidine	No	No
Glycopyrrolate	No	No
Granisetron	No	No
Hyoscyamine	Not applicable	Not applicable
Hyoscyamine extended-release	Not applicable	Not applicable
Infliximab	Yes	Yes
Interferon	Yes	Yes
Lactulose	No	No
Lansoprazole	No	No
Loperamide	No	No
Meclizine	No	No
Mesalamine enema	No	No
Methylprednisolone	No	No
Metoclopramide	Yes	Yes
Misoprostol	Yes	Yes
Nizatidine	No	No
Octreotide	No	No
Omeprazole delayed-release	No	No
Ondansetron	No	No
Pantoprazole delayed-release	No	No
Polyethylene glycol 3350	No	No
Prochlorperazine	No	No
Promethazine	Yes	Yes
Ranitidine	No	No
Ribavirin	Yes	Yes
Sodium phosphate	Yes	Yes
Sucralfate	No	No
Sulfasalazine	No	No
Tegaserod	No	No
Ursodiol	No	No

ketoconazole, itraconazole), was contraindicated. This drug was withdrawn from the market in 2000.

Domperidone

Domperidone, a peripheral dopamine D₂ receptor antagonist, has not been approved by the FDA. Unlike metoclopramide, only a small percentage of this drug crosses the blood–brain barrier. As with cisapride, QT interval prolongation and ventricular tachyarrhythmias have been reported with the use of domperidone. Domperidone causes prolongation of cardiac repolarization by blocking the cardiac potassium current (IKr). This is similar to the therapeutic effects of type III antiarrhythmic agents.

Infliximab, adalimumab, certolizumab pegol, and natalizumab

The monoclonal antibodies infliximab, adalimumab, certolizumab pegol, and natalizumab vary in their composition and target. Infliximab is a chimeric (mouse–human) anti–tumor necrosis factor- α (anti-TNF- α) monoclonal antibody. Adalimumab is a fully human anti-TNF- α monoclonal antibody, and certolizumab is a PEGylated Fab' fragment of a humanized anti-TNF- α monoclonal antibody. Natalizumab is a humanized monoclonal antibody against the cellular adhesion molecule α_4 -integrin.

Because of potent immunomodulating effects, including reduction of immune surveillance, these biologics have the potential to predispose to infection and to enhance development of malignancy. Latent and new tuberculosis infections (frequently disseminated or extrapulmonary), invasive fungal infections, and other, sometimes fatal opportunistic infections have been reported. Lymphoma and other malignancies have also been described. Hepatosplenic T-cell lymphoma in patients receiving biologic agents with or without other immune modulators has been reported (20,21). A review of the AERS database in 2005 indicated that infliximab was the seventh most commonly reported drug associated with death and the third most common drug associated with a disability or serious outcome (13). Infliximab and similar biologic agents have a black box warning regarding a variety of infections and malignancies.

Natalizumab was approved in 2004 for relapsing forms of multiple sclerosis. It was removed from the market in 2005 following reports of progressive multifocal leukoencephalopathy (PML), a viral infection of the central nervous system. Natalizumab returned to the market in 2006 with enhanced warnings and monitoring programs. Through February 2011, 102 cases of PML had been reported worldwide among 82,732 patients treated with natalizumab. A single case of PML has also been reported in a patient with Crohn's disease in the initial clinical trials of natalizumab (22). The estimated incidence of PML is 0.3 per 1,000 patients with fewer than 25 infusions, 1.5 among patients receiving 25–36 infusions, and 0.9 among patients receiving 37–48 infusions.

Summary

Medication safety cannot be completely ensured after drugs enter the market. The FDA has developed the AERS for postmarketing drug surveillance for voluntary reporting of ADRs. Some medications used for gastrointestinal disease have received label changes or have been removed from the market. The FDA is developing new pharmacovigilance methods such as the Sentinel System to improve safety reporting. Health-care providers need to be aware of ADRs associated with the medications they prescribe. Participation in postmarketing surveillance programs will improve safety for our patients.

ACKNOWLEDGMENTS

The following members of the American College of Gastroenterology FDA-Related Matters Committee provided peer review of the manuscript: Costas Kefalas, MD, FACG (Committee Chair); Alan Buchman, MD, MSPH, FACG; Carol Burke, MD, FACG; Tedd Cain, MD, FACG; Jason

Connor, PhD, FACG; John Fang, MD; Ronnie Fass, MD, FACG; Joseph Phillips, MD; Mark Pochapin, MD, FACG; Paul Pockros, MD, FACG; Philip Schoenfeld, MD, MEd, MScEpi, FACG; and Raj Vuppalanchi, MD.

CONFLICT OF INTEREST

Guarantor of the article: Eli D. Ehrenpreis, MD.

Specific author contributions: Eli D. Ehrenpreis, Arthur A. Ciociola, Prasad M. Kulkarni: writing of significant portion of text and preparation of significant portion of bibliography; Eli D. Ehrenpreis: writing of outline, review and modification of various drafts of abstract, submission of manuscript, and revision of original manuscript and preparation of revised manuscript. The FDA-Related Matters Committee of the American College of Gastroenterology identified the need and developed the concept for this article.

Financial support: None.

Potential competing interests: Dr Ehrenpreis serves as a consultant for Pediatric Pharmaceuticals Inc.

REFERENCES

1. Young JH. Drugs and the 1906 law. In: Blake JB (ed). *Safeguarding the Public: Historical Aspects of Medicinal Drug Control*. Johns Hopkins Press: Baltimore, MD, 1970, 147–57.
2. Jackson CO. *Food and Drug Legislation in the New Deal*. Princeton University Press: Princeton, NJ, 1970, 151–74.
3. Federal Food and Drug Act of 1906 (the Wiley Act), Pub. L. No. 59-384, 34 Stat 768 (1906).
4. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 110th Cong., Cong Rec Vol 153 (2007).
5. Wax PM. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann Intern Med* 1995;122:456–61.
6. Calvery HO, Klumpp TG. The toxicity for human beings of diethylene glycol with sulfanilamide. *South Med J* 1939;32:1105–9.
7. Deaths due to elixir of sulfanilamide-Massengill: Report of the Secretary of Agriculture. *JAMA* 1937;109:1985–8.

8. Young JH. The "elixir sulfanilamide" disaster. *Emory University Quarterly* 1958;14:230–7.
9. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat 1040 (1938) (codified as amended at 21 US Cong. 301-392, 1994).
10. Cavers DF. The Food, Drug, and Cosmetic Act of 1938: its legislative history and its substantive provisions. *Law Contemp Probl* 1938;6:2–42.
11. Peltzman S. An evaluation of consumer protection legislation: the 1962 drug amendments. *J Polit Econ* 1973;81:1051.
12. Krantz JC Jr. New drugs and the Kefauver-Harris Amendment. *J New Drugs* 1966;6:77–9.
13. Moore TJ. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. *Arch Intern Med* 2007;167:1752–9.
14. Kenney C, Hunter C, Davidson A *et al*. Metoclopramide, an increasingly recognized cause of tardive dyskinesia. *J Clin Pharmacol* 2008;48:379–84.
15. Chang L, Chey WD, Harris L *et al*. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol* 2006;101:1069–79.
16. Miller DP, Alfredson T, Cook SF *et al*. Incidence of colonic ischemia, hospitalized complications of constipation, and bowel surgery in relation to use of alosetron hydrochloride. *Am J Gastroenterol* 2003;98:1117–22.
17. Lewis JH. Alosetron for severe diarrhea-predominant irritable bowel syndrome: safety and efficacy in perspective. *Expert Rev Gastroenterol Hepatol* 2010;4:13–29.
18. Loughlin J, Quinn S, Rivero E. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. *J Cardiovasc Pharmacol Ther* 2010;15:151–7.
19. Wysowski DK, Corken A, Gallo-Torres H *et al*. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. *Am J Gastroenterol* 2001;96:1698–703.
20. Reddy JG, Loftus EV Jr. Safety of infliximab and other biologic agents in the inflammatory bowel diseases. *Gastroenterol Clin North Am* 2006;35:837–55.
21. Peyrin-Biroulet L, Deltenre P, de Suray N *et al*. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008;6:644–53.
22. Vermersch P, Kappos L, Gold R *et al*. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. *Neurology* 2011;76:1697–704.