

Asthma diagnosis and treatment

Current perspectives

"Black box" 101: How the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk

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A prominently displayed boxed warning, the so-called "black box," is added to the labeling of drugs or drug products by the Food and Drug Administration when serious adverse reactions or special problems occur, particularly those that may lead to death or serious injury. Healthcare providers are often not knowledgeable about the origin, meaning, and implications of these "black box" warnings. In this review, our goal is to provide insight into how the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk. We discuss drug labeling, the emphasis on safety throughout the drug approval process, legislative initiatives for safe use of drugs in children, and postmarketing safety surveillance. In addition, we encourage health care providers to report drug reactions to the Food and Drug Administration's MedWatch program. A discussion of new Food and Drug Administration initiatives to improve drug safety processes and methods to serve the public better are highlighted. (*J Allergy Clin Immunol* 2006;117:34-9.)

Key words: Food and Drug Administration, adverse drug reactions, MedWatch, "black box" warning, drug labeling, drug benefit/risk, risk management, postmarketing surveillance, drug development

It is late on a busy Friday afternoon in your practice and you are ready to write a prescription for Celebrex (Pfizer, New York, NY). You open up your *Physicians Desk Reference* (PDR) to check the dose and notice at the top of the page a warning outlined by a black border—a so-called "black box" warning. You suddenly wonder: (1) what does this warning mean? (2) how did it get there? (3) why is this warning at the beginning of the labeling? and (4) should I prescribe this drug?

Boxed warnings—or, as they have been popularly called, "black box" warnings—are described in the Code of Federal Regulations (CFR) under "Warnings (21CFR 201.57 (e))." This CFR section states:

Abbreviations used

AERS: Adverse Event Reporting System
CDER: Center for Drug Evaluation and Research
CFR: Code of Federal Regulations
DSOB: Drug Safety Oversight Board
FDA: US Food and Drug Administration
IND: Investigational new drug
PDR: *Physicians Desk Reference*
NDA: New drug application

"Labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.... *Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data* [emphasis added]. If a boxed warning is required, its location will be specified by the Food and Drug Administration..."

As physicians/scientists currently employed by the US Food and Drug Administration (FDA), our goal in this article is to give healthcare providers insight into how the FDA evaluates, communicates, and manages drug benefit/risk. To achieve this goal, we briefly cite some of the published literature on "black box" warnings; review the mission and structure of the FDA; and discuss labeling, the emphasis on safety throughout the drug approval process, legislative initiatives for safe use of drugs in children, and postmarketing safety surveillance. In addition, we cover drug risk management programs and encourage physicians to report drug adverse reactions through FDA's MedWatch program. FDA is implementing new initiatives to strengthen drug safety, and we highlight some of these.

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STUDIES OF “BLACK BOX” WARNINGS

Several studies of “black box” warnings have been reported in the literature. In an article analyzing all drugs with a “black box” warning in the 1995 PDR, Beach et al¹ found 206 drugs with a “black box” warning, and these warnings could be grouped into categories. Overall, the most frequent warning ($n = 95$) was for the identification of and avoidance of use in high-risk patients (eg, cigarette smokers and use of oral contraceptives). The next category was information on dosing or drug interactions ($n = 74$). Last were warnings about the need for special training or use in a special setting ($n = 66$; eg, cancer chemotherapeutic agents).

Serious adverse drug reactions, which may result in boxed warnings, commonly emerge after a drug has been approved, marketed, and used in a larger, broader population. A total of 548 new chemical entities were approved during the period of 1975 to 1999 and were examined by Lasser et al.² Of these 548 drugs, 56 (10.2%) acquired a new “black box” warning or were withdrawn from the market: 45 drugs (8.2%) and 16 (2.9%), respectively. By using Kaplan-Meier analysis, these authors estimated that the probability of a new drug acquiring a new “black box” warning or being withdrawn from the market over a period of 25 years was 20%. Further, half of 81 changes to drug labeling occurred within 7 years of drug introduction to the market, and half of the drug withdrawals occurred within 2 years. In an accompanying editorial, Drs Temple and Himmel³ from the FDA report, “Hepatotoxicity has been the most frequent single reason for removing drugs from the market and probably is still the most important single toxicity leading to withdrawal or significant modification of labeling, such as a box warning, that may be recognized postmarketing.”

A recent study evaluated the informativeness and consistency of product labeling of hepatotoxic drugs marketed in the United States. For the 95 prescription drugs including 11 with a “black box” warning, Willy and Li⁴ reported that the information provided in the labeling was variable and affected by many factors, including the perceived level of risk and FDA review division strategy. The mean informativeness score was 35%. However, the score was significantly higher—61%—when the risk was perceived to be high.

FDA BASICS

Dr Steven Galson,⁵ Director of the FDA’s Center for Drug Evaluation and Research, in testimony before Congress stated, “FDA was founded in response to concerns about safety. Attention to safety pervades everything that we do. In the Federal Food, Drug and Cosmetic Act of 1938, Congress gave FDA the authority to review the evidence that a drug was safe for its intended use. In 1962, Congress added a requirement that drug sponsors also demonstrate that a drug is effective, using adequate and well-controlled studies. Thus, drug safety means

that the demonstrated benefits of a drug outweigh its known and potential risks for the intended population and use.”

A brief description of the FDA’s organizational structure provides a context to understand FDA’s current thinking about drug safety, the drug labeling process, and how decisions are made about communicating risk such as placing a boxed warning in a product’s labeling. Internally, the FDA is divided into several centers. The most relevant to clinicians include the Center for Drug Evaluation and Research (CDER), which regulates mainly drug products; the Center for Biologic Evaluation and Research, which regulates blood, blood products, and vaccines; and the Center for Devices and Radiologic Health, which regulates medical devices. CDER is America’s consumer watchdog for medicines, with about 2200 employees, approximately half of whom are physicians or other kinds of scientists.⁶ The safety of drugs is a primary concern throughout CDER. CDER is further divided into several Offices, including the Office of New Drugs. Under the Office of New Drugs are divisions that regulate products in the various therapeutic areas. The asthma and allergy drugs are primarily regulated in the Division of Pulmonary and Allergy Drug Products, which assures that the science supports the efficacy and safety of each drug seeking approval or a new indication. CDER has recently appointed a new Director of the Office of Drug Safety and plans a sustained, multidisciplinary, center-wide approach to drug safety.

WHAT IS IN DRUG LABELING?

A drug label is the written, printed, or graphic matter on the immediate container of the drug product. Labeling includes the product container labels, as well as other written, printed, or graphic information that accompanies the product. The latter may also be referred to as the *package insert* or *product information*. Labeling information can be found in the PDR, at Drugs@FDA.gov, and at the web sites of companies who market the specific drugs. Labeling is the legacy document that accompanies the product.

Labeling (21 CFR 201.56) is a summary of essential scientific information needed for safe and effective use of the drug. It should be informative, accurate, and neither promotional in tone nor false or misleading, and should be based on data derived from human experience whenever possible.

The “Indications and Usage” section of the labeling specifies the indications of the drug supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in 21 CFR 314.126(b). In addition, the labeling should state whether there are safety considerations such that the drug should be reserved for certain situations (eg, refractory to other drugs), conditions that should be met before the drug is used on a long-term basis, and specific tests needed for selection or monitoring of patients who need the drug (eg, liver function tests).

Safety information is found throughout the labeling. The “Contraindications” section (21 CFR 201.57(d)) describes those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit (eg, hypersensitivity to the drug). As described at the beginning of this article, the “Warnings” section (21 CFR 201.57 (e)) describes serious adverse reactions and potential safety hazards and may be in a prominently displayed box in a location specified by the FDA, hence the “black box” warning. The “Precautions” section (21 CFR 201.57 (f)(9)) describes use in special populations such as children. An adverse reaction is defined as an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence and is mentioned in the “Adverse Reactions” section (21 CFR 201.57(g)).

The information included in the labeling is the “true scoop” and, in the opinion of these authors, the closest one can get to the truth regarding the scientific information known about a drug. The information contained in the package insert or product information is the result of careful and extensive analyses performed by the company and then the FDA, using source data. A multidisciplinary team (eg, chemists, pharmacologists, statisticians, and medical officers) carefully reviews the scientific information, and with the sponsor negotiates labeling for a specific drug.

SAFETY EMPHASIS THROUGHOUT THE DRUG APPROVAL PROCESS

The FDA’s focus on safety begins at the earliest stages of drug development. Before beginning any human trials, the sponsor must perform extensive animal toxicity studies.⁷ These animal studies provide information on initial dosing and point to areas of safety needing special attention and monitoring during human studies. FDA’s role in development of a new drug begins when the drug’s sponsor, after screening the new molecule for pharmacological activity and acute toxicity in animals, seeks to test it in humans. The new molecule then changes its legal status and becomes an investigational new drug (IND) subject to specific requirements under the FDA. The IND application must contain animal pharmacology and toxicology studies to assess whether the product is reasonably safe for initial testing in humans. Once the initial IND is submitted to the FDA, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, the FDA reviews the IND for safety to assure that research subjects will not be exposed to unreasonable risk.⁷

Clinical trials are conducted in 3 successive phases to obtain evidence of safety and effectiveness of a new drug for a specific indication.⁷ Phase 1 studies involve the initial introduction of a drug into humans to assess the most common side effects and examine the range of doses that patients can take safely without serious side effects. These studies also provide information on drug kinetics and metabolism. Phase 1 studies are conducted in a small number

of healthy volunteers or, where appropriate, in patients with the disease that the experimental drug is being developed to treat. Phase 2 of drug development involves the earliest controlled clinical trials testing the effectiveness of the drug at various doses for a specific indication in patients with the disease or condition. These closely monitored studies may also identify short-term, relatively common side effects of the drug and usually involve several hundred patients. After phase 2 studies are complete, the FDA and the sponsor usually meet to determine how the drug should be studied in phase 3. The phase 3 studies involve larger numbers of patients, often several thousand, and provide the additional information about safety and effectiveness needed to evaluate the overall benefit/risk relationship of the drug for the condition studied. By having larger numbers of patients exposed for more than 6 months, adverse events may be detected that develop only after a longer exposure.

At the completion of the phase 3 studies, the pharmaceutical company submits a new drug application (NDA) to the FDA and requests the FDA to consider approving the new drug for marketing in the United States.⁷ This NDA should provide enough information to permit the FDA reviewers to reach the following critical decisions: whether the drug has been shown to be effective for its proposed uses; whether safety has been assessed by all methods reasonably applicable to evaluate safety and whether the drug is safe for its intended use—that is, whether the benefits of the drug outweigh the risks; whether the drug’s proposed labeling (package insert) provides adequate directions for use; and whether methods used in manufacturing the drug are adequate to preserve the drug’s strength, quality, and purity. A multidisciplinary FDA team then reviews the NDA over several months to evaluate whether the submitted studies demonstrate that the drug is effective for its proposed use. In addition, the NDA data must demonstrate that the drug has, on the basis of an adequate safety assessment, an adverse event profile that allows a conclusion that the drug is safe for its intended use.

In the course of its review of an NDA, the FDA may convene an Advisory Committee made up of outside experts to provide advice to the FDA. An Advisory Committee may be needed if a drug raises significant safety concerns, is first in its class, or is the first drug for a given indication.

If the drug presents a significant risk or there is a theoretical concern about a safety risk, the sponsor may include in the NDA a proposed risk management plan, tools for risk management, and protocols for further studies. In addition, the FDA may seek a commitment from the sponsor for the conduct of specific postmarketing clinical trials after the drug is approved (ie, phase 4 studies).

LEGISLATIVE INITIATIVES FOR SAFER USE OF DRUGS IN CHILDREN

For decades, children were prescribed medications that had not been studied for safety and efficacy in the

pediatric population. As a component of the Food and Drug Administration Modernization Act of 1997, Congress provided incentives to sponsors to conduct pediatric studies. Section 111 of the Food and Drug Administration Modernization Act of 1997 authorized FDA to grant an additional 6 months of marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conducted the requested studies of a drug in the pediatric population. Using the important information generated by these clinical studies, the labeling for 99 drugs as of October 2005 has been updated to include information on appropriate use of the drug in the pediatric population.⁸

In 2002, Congress renewed this authority when it enacted the Best Pharmaceuticals for Children Act. In addition, the Best Pharmaceuticals for Children Act mandates that during the 1-year period beginning on the date a drug receives pediatric exclusivity, all adverse event reports associated with the use of the drug will be reviewed by FDA and reported to the Pediatric Advisory Committee in a public forum. As of October 2005, adverse events for 46 drugs have been presented identifying new safety concerns, including deaths in children associated with inappropriate use with the fentanyl transdermal system (Duragesic; ALZA Corporation, Mountain View, Calif).⁸

POSTMARKETING DRUG SAFETY SURVEILLANCE

After marketing approval, FDA continues to monitor drug safety through a system of postmarketing surveillance. After approval and marketing, when a drug is used in larger, broader populations for longer durations and for unapproved or off-label indications, previously unidentified adverse drug events often occur. An important drug safety tool for detecting these adverse events is the Adverse Event Reporting System (AERS), which was established in 1969.⁹ This computerized database combines the voluntary adverse drug reaction reports submitted to the FDA by healthcare professionals to MedWatch and the mandatory reports from pharmaceutical companies on adverse events that have been spontaneously reported to the companies, primarily by physicians and pharmacists. These reports may detect early warning signals for potential serious, unrecognized drug-associated events. When a safety signal is detected, specially trained safety evaluators at the FDA search for possible additional cases in AERS, the medical literature, and reports to foreign regulatory agencies. 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. The evaluators 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 (reproducibility of results), and specificity of association.⁹ To confirm the safety

signal, FDA may conduct studies in several large claims databases that link prescriptions with adverse outcomes.⁹ FDA purchases access to commercial databases that contain nonpatient-identifiable information on actual use of marketed prescription drugs in adults and children. This information augments the FDA's ability to determine the public health significance of adverse events reports received by the agency. The ability to detect drug safety signals through spontaneous reports is limited by the low, and highly variable, percentage of events that are reported (as little as 1% of all cases), the uncertain estimates of exposure represented by the number of prescriptions written, and the passive nature of the data collection.¹⁰ In addition to AERS, safety information may emerge from new controlled clinical trials as well as from reports in the literature.

As the FDA becomes aware of new knowledge about a drug's safety profile, risk assessments are undertaken and decisions made about the most appropriate way to manage the new risk. New safety information may be reflected in labeling through new warnings, including in a "black box" when deemed necessary; a risk management program may be implemented; and/or sometimes new safety signals may result in significant changes in the marketing status of the drug such as limited product dispensing or, on rare occasions, withdrawal from the market.

In a recent review of adverse drug event surveillance, the authors report that during the 33-year period from 1969 to 2002, about 2.3 million case reports of adverse events for the cumulative number of approximately 6000 marketed drugs were entered into the AERS database.¹¹ During this period, numerous drug reactions were identified and added to the products as contraindications, warnings including boxed warnings, precautions, and adverse reactions. More than 75 drugs/drug products were removed from the market because of safety problems. In addition, 11 drugs have special requirements for prescriptions or have restricted distribution programs. However, drugs withdrawn or with restricted distribution represent a small proportion (about 1%) of marketed drugs.¹¹

DRUG RISK MANAGEMENT PROGRAMS

The objective of an effective drug risk management program is to allow important drugs to remain on the market by managing potential risks to ensure a favorable risk/benefit ratio. Effective risk management for a drug includes 3 essential components: risk assessment, risk evaluation, and risk intervention/communication. The last component involves the effective communication of modified information regarding the use of a drug product to both professionals and patients.¹²

In May 2004, FDA issued a guidance *Development and Use of Risk Minimization Action Plans* (RiskMAP Guidance) that describes how to address specific risk-related goals and objectives as well as various tools to minimize the risks of drug and biological products.¹²

The risk management of a drug product involves the process of (1) assessing a drug's benefit/risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit/risk balance, and (4) making adjustments to the risk minimization tools to improve further the benefit/risk analysis.¹²

Tools used for drug risk management can be divided into 3 broad categories and are discussed here in increasing order of burden and cost to sponsors, healthcare professionals, and institutions.¹² The first category is "Targeted Education and Outreach." Tools in this category use specific, targeted education and outreach efforts to increase appropriate knowledge about the risks and influence behaviors of key people or groups. Some examples in this category include patient product labeling, medication guides, "Dear Healthcare Professional" letters, FDA alerts, and training programs for healthcare providers or patients. There are very few studies in the literature evaluating the effectiveness of these risk tools. One study reported that a highly publicized "Dear Doctor" letter sent in June 1998 about cisapride was associated with a decline (58%) in the concomitant dispensing rate with explicitly contraindicated drugs. In contrast, an earlier letter about cisapride, although explicit but accompanied by less publicity, had no measurable effect on coprescription.¹³ Another study using a healthcare plan database, showed that a mailed "Dear Healthcare Professional" letter did not effect the rate of coprescribing tramadol with antidepressants.¹⁴

The second category of tools is "Reminder Systems," which include systems that prompt, remind, double-check, or otherwise guide healthcare practitioners and/or patients in prescribing and dispensing, and/or using a product, respectively, in ways that minimize risk. Examples include patient consent forms that involve patient education, including the acknowledgment of reading materials and agreement to follow instructions; healthcare provider training programs that include testing; and limiting the number of doses per prescription or limitation of refills. The third category is "Performance-Linked Access Systems," which link product access to laboratory testing results or other documentation. Examples include administration of the drug only by certified healthcare practitioners (eg, cancer chemotherapy agents by a restricted number of doctors), limited product dispensing only by pharmacies or practitioners who elect to be specially certified, limited product dispensing only to patients with evidence of a specified laboratory result.¹²

MEDWATCH

The FDA administers the MedWatch program that helps promote the safe use of drugs by rapidly disseminating new safety information on the Internet and providing e-mail notification to health professionals, institutions, the public, and FDA's 160 MedWatch partners. In 2004, the FDA issued 50 safety alerts for drugs and therapeutic

biologics and approved 25 to 70 safety-related labeling changes for drugs each month.⁶

MedWatch also provides a mechanism for healthcare professionals and the public voluntarily to report serious adverse events, product quality problems, and product use errors for all FDA-regulated medical products. The adverse events may be reported to the FDA by completing and submitting (by mail or facsimile) the MedWatch form available as the last page of the PDR, by calling (telephone number: 1-800-FDA-1088) or by accessing the MedWatch Internet site (<http://www.fda.gov/medwatch>). We encourage physicians, pharmacists, other healthcare professionals and patients to submit reports of suspected and known adverse drug reactions. The most helpful reports are those 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.⁹ Even a single thorough adverse event report can qualify as a potential signal that requires further research.⁹ In 2004, FDA processed and evaluated more than 400,000 reports of adverse drug events, including 20,000 submitted directly from individuals.⁶ However, a recent study of spontaneous reporting for adverse drug reactions in Germany reported that 75% to 85% of physicians in a survey had never reported an adverse event, and almost 20% did not know about the spontaneous reporting system.¹⁵

As a clinician or consumer, you can find the latest medical product safety information at <http://www.fda.gov/medwatch/>. You can also sign up for immediate e-mail notification of MedWatch safety information at <http://www.fda.gov/medwatch/elist.htm>.

NEW FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

The FDA is constantly striving to improve safety processes and methods to serve the public better. Thus, FDA is taking additional steps to identify drugs that may have unacceptable risk profiles. In 2005, the FDA implemented a new, independent Drug Safety Oversight Board (DSOB), which oversees the management of drug safety issues and provides emerging information to doctors and patients about the risks and benefits of medicines.¹⁶ This board, which consists of FDA supervisors, staff, and medical experts from other agencies in the Department of Health and Human Services and other government departments such as the Department of Veterans Affairs, resolves disagreements over approaches to drug safety issues, assesses the need for MedGuides, and oversees development and implementation of CDER center-wide drug safety policies.

The FDA also has new communication channels to share drug safety information sooner, more broadly, and

more conveniently. These new and direct communication channels will enhance knowledge and understanding of safety issues, and include a Drug Safety Web site (<http://www.fda.gov/cder/drugsafety.htm>) where consumers can find new information on specific drug products, including information sheets for patients and healthcare professionals, the product's regulatory history, and its labeling.¹⁶

To provide earlier information to healthcare providers and patients, FDA has proposed a new Drug Watch Web site where the DSOB can place early emerging drug safety information before the FDA has fully determined whether the drug was responsible. The listing of a drug on the Drug Watch page signifies that FDA is assessing the meaning and potential consequences of emerging safety information.¹⁶

CONCLUSION

Now let's return to the physician who had suddenly come upon a "black box" warning in a drug's labeling.

What does this warning mean? This boxed warning means that there is reasonable evidence of an association of a serious hazard with the drug. A definite causal relationship to the drug does not have to be established. Placing the warning in a box means that the adverse reaction may lead to death or serious injury. Further, the boxed warning is usually based on clinical data, but serious animal toxicity may also lead to a boxed warning when there are not clinical data.

How did the warning get there? For most drugs, a boxed warning appears after the drug has been approved and marketed, thus providing exposure to a large number of patients sufficient to detect a serious, rare event. Often, spontaneous adverse event reports will suggest a safety signal, and further studies may confirm this signal. The FDA may convene a public Advisory Committee to discuss the significance of a safety signal. A newer mechanism for an internal FDA review and discussion of the significance of a safety signal is the DSOB.

Careful consideration is given to placing a "black box" warning in a drug's labeling, and this is always discussed with the sponsor of the drug.

Why is this warning at the beginning of the label? The CFR states that the FDA can specify the location of the boxed warning. Usually the boxed warning is located at the beginning of the labeling so that it stands out and will be immediately seen by a prescriber, who can note the seriousness of the warning.

Should I prescribe this drug? The FDA does not regulate the practice of medicine. All approved drugs have benefit/risk considerations. These should be taken into consideration when prescribing medications to patients. It is up to the individual physician to make this decision.

The FDA has come under criticism, especially over the past 2 years, related to drug safety.¹⁷ In particular, criticism has been directed at FDA's postmarketing surveillance system.¹⁸ FDA has taken measures to strengthen the safety program for marketed drugs, working to be more transparent

in its evaluation of drug safety and communicating drug specific safety risks to healthcare professionals and patients through MedWatch's release of FDA Alerts along with Information Sheets for Health Care Professionals and Patients.¹⁶ In addition, risk management programs using Medication Guides were implemented for 2 drugs in 2004 (Epzicom [GlaxoSmithKline, Research Triangle Park, NC] and Cordarone [Wyeth Pharmaceuticals Inc, Philadelphia, Pa]).⁶ However, research is still needed to implement active surveillance programs for identifying drug adverse events soon after a drug is approved and marketed as well as assessment of the tools that are used to communicate risk of drugs to healthcare professionals and patients. Despite the public criticism of the FDA, it is the view of these authors that the dedicated physicians, scientists, and staff of the FDA continue to work hard every day to protect the health of the American public.

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