

Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs

JUDITH E. BEACH, PH.D.*

GERALD A. FAICH, M.D., M.P.H.**

F. GAIL BORMEL, R.PH.***

FRANK J. SASINOWSKI, M.S., M.P.H.****

I. INTRODUCTION

Prescription drugs are unavoidably associated with adverse effects, but the benefits of using such drugs outweigh the accompanying risks so long as the expert judgment of a licensed practitioner is first applied in the decision to use a drug for a particular patient. Most risks for prescription drugs appear in descending order of importance in the drug's labeling, i.e., the package insert. The Food and Drug Administration (FDA), however, may require special health risks (particularly those that may lead to death or serious injury) to be identified in the labeling in a prominently displayed box or "black box" warning. FDA generally reserves boxed warnings for serious or life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner. A decision by FDA to set apart a particular drug with a black box warning has serious implications for the licensed practitioner, the pharmacist, the patient, the pharmaceutical manufacturer, and the distributor. Nevertheless, FDA has not articulated specifically the scope of studies it relies on or the special circumstances in which the agency would impose this special warning.

To identify FDA's previous practices in order to describe the agency's rationale and bases for imposing the requirement of black box warnings, the authors surveyed 206 black box warnings in package inserts in an attempt to determine both the kind of information the agency sought to impart to the physician and the types of human studies relied upon by the agency.

A. *Legal Background*

Under the Federal Food, Drug, and Cosmetic Act (FDCA),¹ a drug is misbranded if it lacks "adequate directions for use."² Medications that cannot be used safely by consumers without the diagnosis and supervision of a physician are designated as prescription drugs and can be dispensed only on the order of a licensed medical practitioner. FDA's view is that "the primary objective of prescription drug labeling is to provide the essential information the practitioner needs to use the drug safely and

* Dr. Beach is an Associate in the law firm of Hyman, Phelps & McNamara, P.C., Washington, D.C.

** Dr. Faich is a consultant with Pharmaceutical Safety Assessments, Inc., Narberth, PA.

*** Ms. Bormel is Associate Counsel for Scientific Affairs for U.S. Pharmacopeia.

**** Mr. Sasinowski is a Director in the law firm of Hyman, Phelps & McNamara, P.C., Washington, D.C. The authors wish to acknowledge Craig B. Mendelsohn, M.D., J.D., and Christina Ammerman for their contribution in compiling and organizing the data.

¹ Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301 et seq. (1994)).

² 21 U.S.C. § 352(f)(1) (FDCA § 502(f)(1)).

effectively in the care of patients”³ such as “the directions for use and cautionary statements, if any.”⁴

Thus, the manufacturer of a prescription drug is required to provide adequate labeling for practitioners licensed by law to be able to administer or dispense the drug safely and for the purposes for which it is intended.⁵ Therefore, the manufacturer must provide information to the health professional or the so-called learned intermediary,⁶ whose burden it is to decide whether to prescribe the medicine for a particular patient, knowing the risk and benefits associated with the drug.⁷

FDA may determine that a drug is misbranded if the agency finds the labeling as false or misleading⁸ for failing to reveal certain facts material to the customary or usual conditions for use of the drug.⁹ FDA asserts that the FDCA requires that “[a]n adequate warning of possible danger must appear on all [drug] labeling . . . or the product is misbranded.”¹⁰

Thus, in the labeling for any prescription drug, FDA requires that cautionary information be categorized according to the relative severity of the hazard and the degree to which the risk has been substantiated. Accordingly, drug package inserts contain many detailed paragraphs of information about side effects to assist physicians in making prescription decisions. Depending on the relative severity of the hazard, topic headings in prescription drug labeling are set forth in descending order of importance as “Contraindications,” “Warnings,” “Precautions,” and “Adverse Reactions.”¹¹ Therefore, “as known adverse side effects increase in intensity and severity, the manufacturer’s warning in respect to the drug’s potential for harm should accordingly ascend to a higher category.”¹²

B. “Boxed” or “Black Box” Warnings

Although the large majority of prescription drugs have risks reported in the Contraindications, Warnings, Precautions and Adverse Reactions sections of their labeling,¹³ “[s]pecial problems, particularly those that may lead to death or serious injury, may be required by [FDA] to be placed in a prominently displayed box”¹⁴ — a so-called “boxed warning” or “black box warning.” FDA reserves boxed warnings for those risks that best can be minimized by conveying the information to the prescribing doctor in this highlighted manner.¹⁵ Further, boxed warnings are “ordinarily . . . based on clinical data.”¹⁶ Even though FDA may require boxed warnings if there are special problems associated with a drug, particularly those that may lead to death or serious injury,¹⁷ the agency rejected a comment in rulemaking that information re-

³ 40 Fed. Reg. 15,392 (Apr. 7, 1975).

⁴ 21 U.S.C. § 353(b)(2) (FDCA § 503(b)(2)).

⁵ 21 C.F.R. § 201.100 (1997).

⁶ *United States v. Vital Health Prod., Ltd.*, 786 F. Supp. 761, 786 (E.D. Wis. 1992).

⁷ *United States v. Evers*, 643 F.2d 1043, 1052 (5th Cir. 1981).

⁸ 21 U.S.C. § 352(a) (FDCA § 502(a)).

⁹ 21 U.S.C. § 321(n) (FDCA § 201(n)).

¹⁰ 39 Fed. Reg. 33,229 (Sept. 16, 1974).

¹¹ 21 C.F.R. §§ 201.56, 201.57 (1997).

¹² *McFadden v. Haritatos*, 448 N.Y.S.2d 79, 81 (N.Y. App. Div. 1982).

¹³ 44 Fed. Reg. 37,434 (June 26, 1979); 21 C.F.R. § 201.57(d)-(g).

¹⁴ 21 C.F.R. § 201.57(e).

¹⁵ Lars Noah, *The Imperative To Warn: Disentangling the “Right To Know” From the “Need To Know” About Consumer Product Hazards*, 11 YALE J. ON REG. 293 (1994).

¹⁶ 21 C.F.R. § 201.57(e). See also 44 Fed. Reg. at 37,447; 40 Fed. Reg. at 15,397.

¹⁷ 21 C.F.R. § 201.57(e).

lated to clinical benefit or use restrictions for accelerated approval drugs always requires a boxed warning.¹⁸ The agency may refer questions of whether a boxed warning should be included in the labeling of a drug to an FDA Advisory Committee for the particular drug.¹⁹ Although FDA is not obligated to follow recommendations from the Advisory Committee,²⁰ “it usually does.”²¹

For example, FDA has imposed a black box warning in the package insert for Abbott Laboratories’ anti-epileptic drug Depakene® (valproic acid). The warning is based on postmarketing reports of adverse reaction in humans indicating that the drug could cause fatalities, and FDA required the sponsor to warn physicians to monitor patients in order to minimize the risks. Specifically, the black box warning provides in part that:

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID . . . PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS.²²

The further details of serious drug-associated risks as reported in the black box, such as “[t]he frequency of these serious adverse reactions, and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug,” generally are reported elsewhere, such as in the “Adverse Reactions’ Section of the labeling.”²³

Although decisions are made for each new drug independently at the time of its approval, the agency has attempted to achieve some consistency in the labeling for similar prescription drugs. For example, FDA has instituted class-wide labeling changes, including a black box warning for all angiotensin converting enzyme (ACE) inhibitors, such as Accupril® (quinapril), Altace® (ramipril), Capoten® (captopril), Lotensin® (benazepril), Monopril® (fisinopril), Prinivil® (lisinopril), Vasotec® I.V. (enalaprilat I.V.), Univasc® (moexipril) and Zestril® (lisinopril).²⁴ The standardized boxed warning for these drugs states that, “[w]hen used during the second and third trimesters of pregnancy, ACE inhibitors can cause injury and even death to the developing fetus,”²⁵ adding that the drug should be discontinued when pregnancy is detected.

Although FDA’s imposition of a black box warning for prescription drugs has important repercussions for the licensed practitioner, pharmacist, patient, the pharmaceutical manufacturer, and the distributor, FDA has not articulated clearly the

¹⁸ Preamble to New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992).

¹⁹ FOOD AND DRUG ADMIN., POLICY & GUIDANCE HANDBOOK FOR FDA ADVISORY COMMITTEES, ch. XI, Center-Specific Guidance, CDER: Specific Guidance for Topics to Be Presented Before Advisory Committees (1994) (“Consideration of special labeling features, such as boxed warnings, special limitations on use, monitoring requirements, or patient package inserts.”)

²⁰ 44 Fed. Reg. at 37,434.

²¹ K. Gilpin, *Company News: Panel Backs Tagamet Use In Treatment of Heartburn*, N.Y. TIMES, Mar. 28, 1995, at D4.

²² PHYSICIANS’ DESK REFERENCE 414 (49th ed. 1995).

²³ 21 C.F.R. § 201.57(e).

²⁴ ACE Inhibitors Will Be Required to Carry “Boxed Warning,” Food and Drug Admin, Press Release P92-08 (Mar. 13, 1992).

²⁵ *Dangers of ACE Inhibitors During Second and Third Trimesters of Pregnancy*, 22 FDA MED. BULL. 2 (1992); Katie Rodgers, Michael C. Vinson & W. Marvin Davis, *Breakthroughs: New Drug Approvals of 1995 — Part I*, 140 DRUG TOPICS 84 (Feb. 5, 1996).

agency's rationale and bases for setting apart a particular drug with this distinction.²⁶ Therefore, in order to determine the agency's criteria for requiring a black box warning, boxed warnings in package inserts were surveyed and analyzed. In the survey presented in this article, the types of studies on which FDA relies and the kind of information the agency seeks to convey to the prescribing physician in order to minimize serious hazards to patients were noted.

II. METHODS

The authors analyzed all package inserts with black boxes found in the 1995 *Physicians' Desk Reference*.²⁷ First, the authors summarized the type of serious hazards or warnings described in the black box warnings. Next, the nature of the data that supported the statement in the black box was classified.

Based on the analysis, the authors devised a classification scheme for black box warnings as follows:

- where early detection of a side effect by a physician may result in intervention that may reverse the adverse reaction (e.g., valproic acid and hepatic failure);
- where a well-defined subset of patients are at higher risk for the treatment (e.g., pregnant women and isotretinoin);
- where the risks from the treatment with the particular drug may outweigh the benefits in particular circumstances (e.g., aplastic anemia or hepatic failure and felbamate);
- where the dosing/drug interaction is critical to the risk (e.g., fatalities from terfenadine when taken in conjunction with ketoconazole);
- where the physical setting of administration of the drug or the experience and training of the physician is critical (e.g., because of severe toxic reactions, all patients receiving floxuridine should be hospitalized for first course therapy); and
- where the method of administration is critical (e.g., avoiding or treating extravasation of Alkeran).

It was assumed that the black box warning was required by FDA for some drugs based on more than one of these special problems/risks.

Next, the authors classified the type of evidence for supporting a boxed warning into the following categories:

- (1) mainly from controlled clinical trials that were part of the new drug application (NDA) (e.g., HIVID (zalcitabine)); and/or
- (2) by patterns of postmarket reporting (e.g., fatalities from Felbatol® (felbamate)); and/or
- (3) from epidemiological surveys (e.g., cigarette smoking and oral contraceptive use); and/or
- (4) occasionally, some other miscellaneous bases.

²⁶ Without clarification, FDA states only that it may require a boxed warning for "[s]pecial problems, particularly those that may lead to death or serious injury . . ." 21 C.F.R. § 201.67(e). *See also* 44 Fed. Reg. at 37,447-48; 40 Fed. Reg. at 15,397. The agency has issued no guidance relevant to when and why it requires boxed warnings.

²⁷ PHYSICIANS' DESK REFERENCE, *supra* note 22.

These other miscellaneous bases include: drugs determined to have potential for abuse; drugs included in a category that generally are recognized to warrant a specific warning (such as a warning that antihypertensive drugs need periodic reevaluation in each patient and thyroid replacement drugs are ineffective for weight loss); drugs not studied adequately in children or in pregnant women; and drugs shown to be toxic in animals. Because “the boxed warning ordinarily . . . [is] based on clinical data,”²⁸ the authors excluded animal toxicity data in this analysis.

III. RESULTS

A. *Types of Hazards*

As stated, FDA-imposed black box warnings were grouped into six categories (*see* table 1). Overall, the most frequent warning (n=95) was for the identification and avoidance of high-risk patients (e.g., cigarette smokers and oral contraceptive users). This category was followed by information on dosing or drug interactions (n=74). Next were warnings about the need for special training or a special setting (n=66) (these were found particularly for cancer chemotherapeutic agents).

Because several types of warnings often were found in a given black box, the distribution was analyzed by the total number of such warnings. There were a total of 375 warnings contained in the black boxes for the 206 drugs studied, or an average of 1.82 black box warnings for each drug. The distribution of these warnings is given in table 1. Again, avoidance of high-risk patients and dosing/drug interaction information represented the highest relative proportions (25% and 20%, respectively) of all warnings.

Only seventy of the 206 drugs with black box warnings had just one of the six types of warnings. The black box had two warning types for seventy-five drugs, three warning types for thirty-one drugs and four or more warning categories for sixty drugs. For example, Cerubidine® (daunorubicin HCl), an anticancer drug, meets four of these warning categories: the drug’s boxed warning states that it poses a higher risk for patients with impaired hepatic or renal function; the drug must be given into a rapidly flowing intravenous infusion — never by the intramuscular or subcutaneous route; it should be administered only by physicians familiar with leukemia chemotherapy in facilities with laboratory and supportive resources; and, the physician and institution must be capable of responding rapidly and completely to severe hemorrhagic condition and/or overwhelming infection.

A number of drugs have risks for a well-defined subset of patients and dosing and drug interaction issues. For example, for Toradol® (ketorolac tromethamine), a nonsteroidal anti-inflammatory drug (NSAID), FDA requires a boxed warning that its use is contraindicated in nursing mothers because of potential adverse effects on neonates, surgical candidates and patients with suspected or confirmed cerebrovascular bleeding due to platelet inhibition, and patients with advanced renal impairment due to volume depletion. The boxed warning also cautions that dosage should be adjusted for patients sixty-five years or older and for patients under 110 pounds. In addition, the drug is contraindicated in patients currently receiving other NSAIDs because of the cumulative risk of inducing serious NSAIDs-related side effects.

Some of the warning classifications are related closely and may be difficult to distinguish from one another. The following example illustrates the subtle differences

²⁸ 21 C.F.R. § 201.57(e).

between a high-risk subset and a question of risks outweighing benefits. Koate®-HP (antihemophilic factor, human) is a product prepared from pooled human plasma, and is indicated for the treatment of classical hemophilia. Hemophiliacs who have had little exposure to blood products, as a group, have a higher risk of developing hepatitis from this product. On the other hand, depending on the severity of the hemophilia, the risk for some hemophiliacs may be greater than the benefits of the product. The black box warns that the physician should weigh the risk/benefits for this product with the severity of the patient's condition.

B. *Nature of Evidence/Data*

Of the 206 prescription drugs with black box warnings, the warning appeared to be based on a combination of sources in many instances (*see* table 2). Thus, there were 254 sources of evidence drawn upon for the 206 warnings, or 1.23 sources per black box (table 2). The most frequent source was postmarketing reports (52%) followed by clinical trial data (29%). Epidemiological studies (9.4%) were cited particularly for hormonal products, while other sources accounted for 9.4% of the evidence used for the basis of the warning given.

IV. DISCUSSION

The study indicates that FDA seems to have established a pattern of practice for imposing black box warnings on drugs. Of the 206 drugs examined with black box warnings, the vast majority were supported by the incidence of adverse events in controlled clinical trials as part of the NDA, or were based on postmarketing surveillance reports, or both. Those drugs with black box warnings supported solely by large-scale or multiple epidemiological studies were limited to special situations such as cigarette smoking and oral contraceptive use.

The authors have determined that six criteria describe when black boxes have been used by FDA to convey critical information to the prescribing physician. In the majority of cases, the survey indicates that FDA imposes a black box warning when there is more than one message or concern. From the analysis, and as described in the Methods section, the concerns are summarized as follows:

- (1) early detection of a side effect by physicians may result in intervention that may reverse the adverse reaction;
- (2) a well-defined subset of patients are at higher risk for the treatment;
- (3) the risk from the treatment of the particular drug may outweigh the benefits in particular circumstances;
- (4) the dosing or drug interaction is pivotal to the risk;
- (5) the training of the physician or the setting is crucial; and
- (6) there are other special requirements for administering the drug.

Whether FDA imposes a requirement that certain information be included in a black box has important ramifications for the licensed practitioner, the pharmacist, the patient, the pharmaceutical manufacturer, and the distributor. The labeling of a prescription drug "plays a role in influencing medical judgment" and is considered "the most reliable guide for health care professionals using a drug in the daily practice of medicine."²⁹ The practitioner, when deciding to use a drug, should be able to look

²⁹ Thomas Scarlett, *The Relationship Among Adverse Drug Reaction Reporting Drug Labeling, Product Liability, and Federal Preemption*, 46 FOOD DRUG COSM. L.J. 31, 33 (1991).

to the boxed warnings for information about life-and-death risks associated with drugs and for ways to minimize these risks. It is therefore critical that FDA's decision to require a black box be fair, reasoned, and based on its established criteria. Otherwise, the physician's decision may be prejudiced against a drug that, in fact, may be the ideal choice for treating a particular patient's disease or condition.

It is imperative that the prominence of a warning be proportionate to the risk and supported by data. If the seriousness of the information in the boxed warning is exaggerated, practitioners and pharmacists may become skeptical so that their confidence and reliance on such information will diminish. Indeed, concerned that the importance of the information in a black box does not become diluted, FDA has emphasized that, "to ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by FDA."³⁰ Even when present, a black box warning may not always be heeded. For example, despite a class-wide boxed warning stating that synthetic thyroid products were ineffective and potentially dangerous for weight loss, its use for this purpose persisted.³¹

There are also marketing considerations for the pharmaceutical manufacturer. The addition of a black box warning to a drug's labeling can have a profound effect on the sales of the drug. For example, during the year after FDA required a black box warning for Seldane® (terfenadine), cautioning against its use in certain settings, particularly with drugs that inhibit its metabolism in the patient,³² the product's "sales dropped from around \$700 million to \$450 million."³³

With patients' increased access to drug information in the *Physicians' Desk Reference* and elsewhere, it is essential that warnings highlighted in a black box are indeed serious enough to warrant such prominence. Indeed, there are several known adverse consequences to patients made aware of drug-associated risks, such as increasing patients' reporting of side effects, but not the accuracy of the reporting,³⁴ and "compromis[ing] rather than enhanc[ing] patient compliance."³⁵

A black box has implications for product liability as well. Some courts have determined that a black box warning sufficiently warns a physician of a drug-associated risk, protecting the manufacturer from product liability pursuant to the "learned intermediary rule."³⁶ With such significant effects of black box warnings, it is critical that FDA carefully consider the ramifications of imposing such an important warning.

³⁰ 44 Fed. Reg. at 37,434.

³¹ S.C. Kaufman, T.P. Gross & D.L. Kennedy, *Thyroid Hormone Use: Trends in the United States From 1960 Through 1988*, 1 THYROID 285 (1991).

³² FDA Request Marion Merrell Dow to Warn Doctors, FDA Press Release P92-22 (July 7, 1992); Thompson and G. Oster, *Use of Terfenadine and Contraindicated Drugs*, 275 JAMA 1339 (1996).

³³ Jennifer Mann Fuller, *Drug Stung by Rivals, New Label; Competitors Moved in as Warning Was Added to Seldane*, KAN. CITY STAR, May 30, 1996, at B1.

³⁴ Ivan Barofsky, *Potential Effects on the Health Care System - I, Joint Symposium on Drug Information for Patients: The Patient Package Insert*, 11 DRUG INFO. J. 71S, 73S (Jan. 1977) ("We can never have the situation where we improve our ability to recognize dysfunction . . . without also increasing the chances of a false alarm."). Also, "evidence indicates that listing possible side effects of drugs increases the probability that patients will report them, even when they are in fact taking placebos." Richard Dorsey, *The Patient Package Insert: Is It Safe and Effective?*, 238 JAMA 1936, 1938 (1977) (citing K. Rickels and R.W. Downing, *Side Reactions in Neurotics: II. Can Patients Judge Which Symptoms Are Caused by Their Medication?*, 10 CLIN. PHARMACOL. 298 (1970)).

³⁵ See B. Blackwell, *Drug Therapy: Patient Compliance*, 289 N. ENG. J. MED. 249 (1973).

³⁶ *Hammock v. Hoffmann-LaRoche, Inc.*, N.J. Super. Ct. A-124 Sept. Term 1994, DDS No. 52-1-6305 (decided Aug. 2, 1995) (determining that Hoffmann-LaRoche's black box warning sufficiently informed physicians prescribing Accutane® of the drug's potential to cause birth defects); Margaret Gilhooly, *Learned Intermediaries, Prescription Drugs, and Patient Information*, 30 ST. LOUIS U. L.J. 633 (1986).

Several limitations in the methods used in this survey should be noted. The authors did not examine the NDA data and have used “best judgment” to deduce the source of the evidence used to support the warnings given in the black boxes studied. No attempt was made to separate the initial labeling from revisions appearing subsequently and so comment cannot be made on the evolution of individual labels over time. Lastly, the authors did not attempt to analyze the differences in FDA use of black boxes in recent years compared with earlier years.

V. CONCLUSION

The results indicate that FDA reserves black box warnings generally for those situations in which 1) there is a strong clinical database to define the risk or hazard, and 2) the medical practitioner’s attentiveness to the highlighted risk has important clinical significance that requires the judgment of that practitioner. Although FDA has not declared explicitly the nature and scope of the agency’s bases and rationale for requiring black box warnings, from their analyses, the authors have determined that the agency seems to have established patterns of practice for imposing the highlighted warnings in certain cases. FDA seems to require such warnings for serious or life-threatening drug-associated risks that are well established and well defined, supported in nearly all cases by the incidence of such events in controlled clinical trials that are part of the NDA, and/or based on patterns of postmarket reporting.

FDA imposes the warnings in order to convey life-and-death information to the prescribing doctor,³⁷ who is in a position to minimize the risks to the patient. From the analyses, one reaches the conclusion that the agency has multiple rationales for imposing the boxed warning:

- to ensure that the prescribing doctor has the necessary information to perform risk/benefit analyses for the specific patient in particular circumstances;
- to ensure safe and effective dosing of the drug;
- to secure crucial methods and settings for administration of the drug;
- to reduce dangerous drug interactions; and
- to promote the monitoring of patients for serious, but possibly reversible, adverse reactions.

Placing a warning for a prescription drug into a black box, if unwarranted, dilutes the importance of all such warnings, and creates inconsistency with other marketed products. With patients’ increased access to drug information, it is essential that warnings highlighted in a black box are indeed serious enough to warrant such prominence. Because of several adverse consequences to patients made aware of drug-associated risks, it is imperative that these prominent warnings are sanctioned by the agency’s established patterns of practice as described herein.

³⁷ 21 C.F.R. § 201.57(e)

TABLE 1

**Distribution of 375 Warnings contained in Black Boxes
by Type for 206 Drugs***

Type of Warning	Numbers	375 Warnings (%)	206 Drugs (%)
Early detection of a reversible condition	47	12%	23%
Avoidance of high risk patients	95	25	46
Risks outweigh the benefits in specific circumstances	36	10	18
Dosings or drug interaction information needed to avoid the hazard	74	20	36
Special training or physical setting is needed	66	18	32
Special information on drug administration	57	15	28
TOTAL	375	10%	18%

* There was an average of 1.83 black box warnings in each blackbox for each of the 206 drugs.

TABLE 2

Evidence Used for Black Boxes for 206 Drugs

Type of Evidence	Number*	(%)
Clinical Trials	73	28.7
Postmarket Reports	133	52.4
Epidemiology Studies	24	9.4
Other	24	9.4
Total	254	100

* 1.23 sources per black box