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Law: Dissemination of Risk Information: What's in That Black Box?

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AN ONGOING CE PROGRAM
of the University of Connecticut School of Pharmacy and Pharmaceutoical Sciences

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists and pharmacy technicians will be able to

- Characterize the different risk management strategies used by the FDA
- Describe how FDA warnings affect healthcare practice
- Review how warnings are developed and applied

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TARGET AUDIENCE: Pharmacists and pharmacy technicians who want to brush up on federally-required risk management labeling.

ABSTRACT: All drugs have risks and patients encounter many sources, both reputable and questionable, to receive information about these risks. This continuing education activity will review some of the programs created by the Food and Drug Administration to warn about potential adverse events related to drug use. The emphasis is on boxed warnings, Patient Package Inserts, Risk Evaluation and Mitigation Strategies, and Medication Guides. The activity will review the characteristics and development of these programs, their statutory basis, and their effect on prescribing.

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INTRODUCTION

A woman is anxiously waiting at the pharmacy counter and asks to see the pharmacist. She hands you a container and says, "I picked up this prescription for my father yesterday and I noticed this big black box on the patient information." There is indeed a visible big black box that surrounds a message saying "WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS." "What should I do?" she asks, "and why didn't someone talk to me about this when I picked up the prescription?" You think back and remember that this is called a "boxed warning"…

THE BOXED WARNING

The Food and Drug Administration (FDA) has several means of providing information on drug risks to healthcare practitioners and patients.[1] One example is the boxed warning (BW, formerly and colloquially referred to as a "black box warning"). The FDA requires a BW for certain medications and reserves them for the most serious risks associated with a drug.[1] It is intended "to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management."[2] A BW is designed to alert healthcare providers and patients to potentially fatal or serious life threatening or disabling adverse effects that may occur with the use of that drug.[3]

A BW is ordinarily used in situations where[1]

- an adverse reaction is so serious in proportion to the potential benefits that it is essential that prescribers consider the risk/benefit before prescribing
- there is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug
- the FDA has concluded that the drug can be safely used only if its distribution or use is restricted.

Appropriate use of the drug in this context includes patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug, or managing patients in a specific manner.[1]

A BW provides a brief, concise summary of the information that is critical for prescribers to consider before providing it to a patient and includes any restriction on distribution or use.[1] Typically, a more detailed description of the risk is included elsewhere in the labeling (e.g., in contraindications or warnings and precautions sections), that must be identified by a cross-reference.[1]

BWs have a required format. The information within the box must not exceed 20 lines, must be arranged in bullet points, and must be preceded with a bold, uppercase header containing the word "**WARNING**" and identify the subject of the warning.[2] The bolded heading and summary must be contained within the box and must be followed by the statement "See full prescribing information for complete boxed warning."[2] The standardization of the BW results in a uniform, easily recognizable warning, ensuring that safety information is easily accessible for its intended audience without confusion.[4]

The FDA's Center for Drug Evaluation and Research (CDER) ordinarily determines whether to require a drug to carry a BW. The decision is usually based on clinical data, but serious animal toxicity may also be the basis of a BW in the absence of sufficient clinical data.[4] CDER usually seeks the advice of an advisory committee before issuing a warning. CDER is not bound by the committee's recommendation but usually defers to their advice.[4]

Approval of a new drug by the FDA may be contingent upon the addition of a BW. Alternatively, the manufacturer may add the warning after marketing if post-marketing surveillance detects a serious adverse effect.[5] The FDA continuously monitors data from post-marketing surveillance, such as MedWatch, and may modify the warning if it is warranted.[3]

While the FDA mandates the warning, the drug manufacturer often drafts and incorporates it into the product's labeling subject to FDA approval.[6] Typically, the sponsor submits initial labeling which the FDA reviews and is subject to negotiation; there is a 30-day period during which the agency and the drug sponsor can exchange viewpoints and suggest alternative language.[6] The FDA may request edits and clarification or additional studies. The FDA may also insist on narrowing the approved indications for the drug or limit it to severe cases of the approved indication. If the FDA and the manufacturer cannot reach an agrreement, the FDA is authorized to make the final determination.[6] Moreover, the manufacturer may not issue a BW without prior FDA approval.[7]

Healthcare professionals should recognize that the BW is the result of a regulatory judgment and emerges from consideration of factors such as clinical trial data, post-market surveillance, mechanistic plausibility, expert opinions, and other subjective factors; it is not based on an objective or systematic standard or threshold.[8,9] The determination about a warning may be based on observed harms or anticipated harms, such as risks associated with pharmacologically similar drugs or plausible risks that have not yet been substantiated with current use.[8]

Drug manufacturers have an incentive to resist labeling their product with a BW since a BW may affect the prescribing of a drug, especially if alternatives exist that do not have a prominent warning.[9,10] One example is the use of atypical antipsychotic drugs (such as the one our patient above inquired about). One study examined the prescribing of atypical antipsychotic drugs before and after an FDA advisory leading to a subsequent BW in 2005. The BW warned of an increased risk of mortality associated with the use of atypical antipsychotics among elderly patients with dementia.[10] Use of atypical drugs had increased at an annual

rate of 34% during the two years prior to the BW. The advisory and BW were associated with a decrease in the use of these drugs beginning within one month of the advisory and continuing at least through 2008.[10]

Similar declining sales were observed for droperidol and antidepressants in children.[9] A mail survey of 2,400 pediatricians in Canada conducted after a warning was required for selective serotonin reuptake inhibitor antidepressants found that about three-quarters of prescribers were aware of the warning and 80% of those changed their prescribing habits.[11] About one-third of prescribers aware of the warning followed their patients more closely and 7% stopped treatment with these drugs in at least one patient.[11]

An interesting tale of the effect of a boxed warning occurred with droperidol.[12] The FDA approved droperidol in 1970 as an antiemetic and tranquilizer and prescribers used it effectively to prevent and treat postoperative nausea and vomiting. In the late 1990s, reports indicated the drug had the potential to produce cardiac complications, including QT interval prolongation, ventricular arrhythmias, and Torsades de Pointes. The FDA mandated a BW in 2001 because of the heart complications.[12]

The warning label stated that patients should be given droperidol only after failing other treatment options and also stated that prescribers should use electrocardiography prior to drug administration and continue for two to three hours afterwards to monitor cardiac arrhythmias.[12]

Following this decision, droperidol use dropped as hospitals and clinicians switched to safer alternatives that required less monitoring. The drug virtually vanished from hospital pharmacies and formularies.[12] This resulted in strong reaction from the medical community. Critics pointed out that the scientific evidence to support the BW consisted of a few hundred patients receiving varying doses of droperidol, with the vast majority of patients far exceeding the usual antiemetic dosing by as much as two orders of magnitude.[12] Most patients who suffered fatal complications had received droperidol doses of 25 to 250 mg, compared with the lower standard intravenous antiemetic dose of 0.625 to 1.25 mg. Moreover, many of the patients who received droperidol doses of 1.25 mg or less and experienced cardiac complications had confounding factors present, which were not accounted for by the FDA.[12]

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Independent reviews of the FDA's data concluded that droperidol's safety and efficacy at lower doses was comparable to alternatives, but the FDA refused to drop the warning label.[12,13] In 2003, the FDA noted that it had asked the manufacturer to undertake additional safety studies or submit an extensive literature review.[12] The drug manufacturer rejected this request, citing financial constraints. However, the FDA provided further clarification that the BW was only meant to apply to droperidol doses specified in the package insert, which was an initial dose of 2.5 mg, since that was the only data available to the agency.[12] The FDA could not assess the safety and efficacy of the lower antiemetic dose and considered this to be an off-label use.[12] The FDA reasserted that it does not regulate off-label drug use as deemed appropriate by a clinician's professional judgement. Subsequently, the drug regained some use in emergency departments.[12]

PAUSE AND PONDER: How can you balance providing important risk information while not instilling reluctance to use a medication when counseling?

The BW is not permanent. Warnings can be removed or modified (see below) if new, robust scientific evidence shows the risks are overstated or don't apply to current patient populations.[3,8] Some circumstances that would justify removal of a BW include conclusions based on outdated or flawed original studies; better follow-up studies that show a more favorable risk/benefit relationship; warnings that overstate the risk and result in patients avoiding needed treatments; or advocacy from medical organizations.[3]

BACKGROUND

The boxed warning was first implemented in 1979 and currently, more than 400 products carry the warning.[5,9] One analysis determined that the estimated probability of acquiring a new boxed warning or being withdrawn from the market over 25 years was 20%.[14] Many serious adverse drug reactions are not identified until after FDA approval, and a drug's safety profile often remains uncertain for several years on the market.[14]

A study of 222 drugs approved between 2001 and 2010 found that 123 resulted in postmarket safety events sufficient to trigger a regulatory response; 61 of these were BW, 59 were safety communications, and three drugs were withdrawn from the market.[15] The median time from approval to first postmarket safety event was 4.2 years.[15] Eight of the BWs were preceded by a safety communication but only four of these safety communications described the safety risk that triggered the

subsequent BW.[15] Biologics and psychiatric medications were the most likely to receive a warning.

Drugs that were given FDA fast-track approval status were more likely to receive a boxed warning.[15,16] One study found that fast-tracked drugs were 3.5 times more likely to receive a BW after already being prescribed to patients.[16] The study, looking at 200 approved drugs, found that 30 received a BW and 11 were eventually withdrawn due to safety concerns.[16]

Familiar examples of drugs requiring a BW include atypical antipsychotics (such as the one the woman asked the pharmacist about), antidepressants, opioids, benzodiazepines, anticoagulants, non-steroidal anti-inflammatory drugs, isotretinoin, certain antibiotics, and biologics.[3]

An early example is the antibiotic, chloramphenicol. Chloramphenicol received a black box-like warning in 1961 before the 1979 regulations were enacted due to concerns over an adverse effect: fatal aplastic anemia (a rare life-threatening hematologic condition marked by bone marrow failure and subsequent low levels of red and white blood cells and platelets in the blood).[17] The FDA first warned prescribers through other types of label modifications, but inappropriate use of the drug continued, prompting the FDA to issue its first box-like warning.[17] The warning was directed to prescribers and appeared in the Physician's Desk Reference, without direct communication to patients.[18]

When a BW is warranted, the FDA usually requires it for all members of a drug class.[3] The rationale is that the characteristics necessitating the warning are usually shared by different pharmacologically similar therapeutic agents. However, there are also circumstances where a BW is not universal for all drugs in a category; for example, two pharmacologically similar drugs may have different pharmacokinetic profiles.[9]

A boxed warning can also be applied when a drug poses risk-benefit considerations that are unique among drugs in a class.[1] It is important to identify when a drug is uniquely associated with a particular risk and is therefore designated as a second-line therapy for that reason.

Although the BW is intended to warn prescribers, pharmacists, and patients, many researchers and clinicians question this labeling approach's effectiveness.[5] One study of hospital residents and attending physicians found that they had a limited knowledge of which medications carried BWs and the content of the warnings.[5,] Needless to say, this may put patients at risk.

Another study investigated how frequently physicians prescribe BW drugs and whether they do so in compliance with the warnings. The study used automated claims data from almost one million U.S. patients from 10 geographically diverse health plans.[19] They found that over a 30-month period, the range of compliance with BWs among prescribers varied from 0.3% to 49.6%.[19,20] More than 40% of health plan enrollees received at least one medication that carried a BW that could potentially apply to them. Most prescriber non-compliance occurred with recommendations for baseline laboratory monitoring. The authors speculated that the lack of consensus regarding the value of laboratory monitoring, for example of liver function testing in preventing drug-induced liver failure, may explain why some physicians choose not to monitor some laboratory results, given the limited evidence supporting their effectiveness.[20] In contrast, they found few instances of prescribing BW drugs to pregnant women that were absolutely contraindicated in pregnancy.[19,20] The authors commented that evidence shows that BWs may not adequately function as risk communication tools so consequently, the FDA and manufacturers increasingly implement strengthened risk management programs for certain drugs.[20]

OTHER RISK MANAGEMENT PROGRAMS

The FDA has other risk management programs in addition to BWs.[21] The Durham-Humphrey Act of 1951 may be considered the first risk management program, since it established the requirement that certain prescription drugs could only be used under the supervision of a licensed healthcare practitioner.[21] (Prior to the act, the manufacturer decided if its drug would be prescription or OTC.) In the 1980s, the FDA occasionally asked companies to develop special safety programs called Risk Management Programs (RMPs) or Risk Minimization Action Plans (RiskMAPs) to mitigate serious risks for a limited number of drug products that offered substantial therapeutic benefits.[21] These programs consisted of education for patients and providers and distribution restrictions.[21,22]

Some other current risk management programs include Patient Package Inserts (PPIs), the Risk Evaluation and Mitigation Strategy (REMS), and Medication Guides (MGs). FDA's primary risk management tool is communication through FDA-approved product labeling for healthcare providers and patients.[21] The FDA considers labeling to be sufficient to ensure that benefits outweigh the risks for most drugs. However, the FDA may determine that additional precautions, such as REMS, are needed in a limited number of cases.[21]

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Patient Package Inserts

The forerunner to the boxed warning was the now-familiar PPI which was first put into place in 1970 for oral contraceptives (OC) and expanded in 1977 to include estrogen-containing drugs.[23,24] The PPI includes a warning regarding the most serious adverse effects of drugs and is required to be placed in or accompany each package dispensed to the patient.[23] The FDA's rationale for mandating direct information to patients was based on the elective nature of OC use by otherwise healthy women and the potential for serious (sometimes fatal) adverse effects.[25] The inclusion of a warning to patients also provided an opportunity for patients to participate with physicians in making a decision about their therapy.[25] The agency's action came as a result of several studies published in 1970s that indicated an association between the use of conjugated estrogens and an increased risk of endometrial cancer in women. A recommendation by the FDA's Obstetrics and Gynecology Advisory Committee also contributed to the decision.[26]

The institution of the PPI prompted litigation.[26] The Pharmaceutical Manufacturers Association and others, including the National Association of Chain Drug Stores, sued the FDA alleging that the Food Drug and Cosmetic Act (FDCA) did not grant the authority to make these types of requirements and that the PPI interfer with the physician-patient relationship.[26]

The court rejected these arguments. The judge ruled that the FDCA does provide the FDA with authority to require these warnings and concluded that when the FDA "determines that the possible side effects of a drug when used as customarily prescribed are sufficiently serious as to be material to the patient's decision on use of the drug, he or she may require disclosure of those side effects on the labeling."[26] Moreover, the court agreed with the FDA's point that new studies showing that estrogen may be "unsafe for use" under the conditions explained in the labeling justified the development of the PPI since labeling that did not disclose the risks involved would be misleading.[26]

The manufacturers asserted that, "requiring the physician to communicate information emanating from Washington without regard to his or her professional judgment concerning the accuracy of the advice or the desirability of the patient being exposed to it" interfered with the physician-patient relationship.[26] The court reasoned that the requirement does not preclude a physicians from exercising their judgement since they are "free to discuss the matter fully with the patient, noting his own disagreement and views" and that the labeling requirement actually encourages this behavior. The court stated that the manufacturers "urge recognition not of a right to exercise judgment in prescribing treatment, but rather of a right to control patient access to information."[26]

It is also worth noting the messages submitted to the FDA during the public comment period prior to the enactment of the PPI.[25] The agency received more than 1,000 comments with consumer groups supporting the development of warning labels.[25] The comments revealed that patients often do not understand the language healthcare professionals use. Further, patients exposed to oral information usually are not attentive to it, often do not remember it, and are unwilling to ask for clarification.[25]

PAUSE AND PONDER: How do you think these findings from 1975 would be applied today? In what ways are they (or aren't they) still relevant?

The FDA initially proposed requiring PPIs for 50 to 75 drug classes during a pilot phase, with plans to expand the requirement to nearly all prescription drugs afterward.[25] Obviously, this has not yet occurred.

Risk Evaluation and Mitigation Strategies

Another warning that the FDA uses to alter patient behavior impact pharmacists and technicians: the REMS. REMS are designed to help reduce the occurrence or severity of a particular serious adverse event produced by a drug and may go beyond mere communication.[27] FDA can require a REMS for prescription drugs and biologics if the agency determines a warning is necessary to ensure that the benefits of the medication outweigh the risks. These medications would not be approved—or would be withdrawn—without a REMS due to their known or potential serious risks.[27]

The FDA's authority to require REMS was established by the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA).[28] The FDAAA expanded the FDA's authority to manage risks. The FDA's practice already included most of the REMS elements, but the new law created the authority to utilize risk evaluation and mitigation strategies and provided for structure, enforcement, and dispute resolution.[22] Prior to FDAAA (before 2007), 16 drugs were approved with restrictive risk management programs, including clozapine (the "No Blood, No Drug" program) and thalidomide (the "System for Thalidomide Education and Prescribing Safety" program, or S.T.E.P.S.).[22]

Table 1. Possible Prescribing Restrictions Associated with ETASU[29]

- Prescribing may be limited to healthcare providers who have a particular training or experience or are specially certified
- Dispensing only from certified pharmacies or healthcare settings or restricted to certain settings such as a hospital
- Dispensing restricted to patients subject to monitoring or who provide evidence of safe use conditions such as a laboratory test
- Enrollment in a patient registry

In determining whether REMS is necessary, the law requires consideration of the following factors[29]:

- the estimated size of the population likely to use the drug involved
- the seriousness of the disease or condition that is to be treated with the drug
- the expected benefit of the drug with respect to such disease or condition
- the expected or actual duration of treatment with the drug
- the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- whether the drug is a new molecular entity

A REMS is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks.[29] If the FDA determines that a REMS is necessary, it may require additional resources describing the risks including a PPI or a MG (see below).[29] They may also require "elements to assure safe use" (ETASU) as part of a REMS if the documentation is not adequate to mitigate a serious risk.[29]

ETASU may include one or a combination of the restrictions described in **Table 1**.[29]

FDA's determination as to whether a REMS is necessary for a particular drug is a drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how each component applies in a particular case.[29] In conducting this analysis, FDA evaluates whether "any drug-specific risks outweigh the drug's benefits and whether additional interventions beyond FDA-approved labeling are needed to ensure that its benefits continue to outweigh its risks."[28] FDA relies on both premarketing and postmarketing risk assessments in making the determination. Pharmacy employees can consult FDA's website (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm) to view which drugs currently require a REMS.

While FDA determines that a REMS is necessary, specifies the requirements, and approves the specific programs, the drug's manufacturer is responsible for developing and implementing the program.[27] Some manufacturers develop these programs themselves while other manufacturers hire vendors or other companies to develop and implement the programs on their behalf.

The law requires that when a drug has a REMS, any generic equivalents for these drugs must also have a REMS.[27] Sometimes, the brand name manufacturer and the generic version's manufacturer jointly develop and implement a REMS (referred to as a "shared system REMS"). At other times, the brand name drug and the generic have different REMS, but both must meet the same goal(s) and requirements.

The law permits waiving REMS distribution or use restrictions for certain medical countermeasures during a declared public health emergency and establishes a pathway to ensure access to REMS restricted drugs for off-label use in serious or life-threatening conditions.[29] It does not appear that the FDA has ever exercised this option.

REMS can affect healthcare practitioners and patients in many ways.[30] Some medications with a REMS can only be dispensed in specific healthcare settings, such as hospitals or infusion centers. Many REMS do not require pharmacists to do anything outside of their normal dispensing activities. However, for certain REMS, pharmacists and other dispensers may need to complete certain requirements in order to dispense the drug. These may include completing training, verifying safe use conditions (e.g., verifying required laboratory monitoring or that a patient or healthcare provider is enrolled in the REMS), counseling patients, and/or providing the patient with educational materials or a MG prior to dispensing a medication with a REMS.[30] Certain REMS may require the pharmacies to become certified. For example, the anticonvulsant vigabatrin is only available in an inpatient setting or from pharmacies that are able to comply with the REMS' requirements. Another example is mifepristone, discussed below.

Some drugs require both a BW and a REMS. Pharmacists and technicians have probably encountered the dual warnings for

isotretinoin. The FDA approved isotretinoin for the treatment of severe acne in 1982.[22] Isotretinoin is highly teratogenic and the FDA issued multiple warnings against the use of the product during pregnancy: in three sections of the package insert (warnings, precautions, and contraindications) and also in a patient information brochure and in information to prescribers.[22] Shortly after approval, reports of human malformations emerged in patients taking the drug. As a result, health communication letters were sent to 500,000 prescribers and 60,000 pharmacists reminding them about the warnings on the package insert. The 1982 warning was sufficient to inform users of the dangers from the drug and also provided protection for the manufacturer to avoid liability, at least according to the Florida Supreme Court.[31]

In 1988, following a meeting of the Dermatologic Advisory Committee, warnings were upgraded and an isotretinoin Pregnancy Prevention Program (PPP) was implemented; this was the first risk management program introduced by a pharmaceutical company.[22,31] The program included several elements: a boxed warning; informed consent for female patients; a PPP kit for physicians containing patient information brochures and pregnancy counseling materials for the prescriber; a prescriber tracking survey; and annual and quarterly meetings with FDA.[22]

Pharmacy personnel are aware that isotretinoin also has a REMS designation, the iPLEDGE program.[32] The iPLEDGE Program was originally implemented in early 2005 and approved as the iPLEDGE REMS in 2010. The goal of the REMS was to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions and prevent fetal exposure to the drug. One of the REMS requirements is that prescribers must be enrolled, and the dispensing pharmacist must receive a Risk Management Authorization (RMA) before filling and dispensing prescriptions.[32]

Isotretinoin has also been associated with an increased risk of neuropsychiatric adverse events including depression, anxiety, and increased suicidality.[33] These risks prompted the FDA to issue a BW in 2005, but these observations have been refuted.[33]

Another example of a drug that carried both a boxed warning and a REMS is the atypical antipsychotic drug, clozapine. The FDA approved clozapine for treatment-resistant schizophrenia in 1989 and its labeling included a warning due to a risk of producing severe neutropenia.[34] The initial requirement called for weekly white blood cell monitoring. The requirement was revised in 2005 to weekly monitoring for the first six months of therapy, biweekly monitoring for months six to 12 months, and monthly monitoring therafter.[34] The monitoring protocol formally became a REMS in 2015.[35] The REMS was lifted in 2025 as a result of evidence suggesting that the risk is no greater than for other antipsychotics and a decision by FDA to decrease the burden on the healthcare delivery system and improve access to clozapine.[35,35]

Clozapine and most other second-generation antipsychotic drugs also carry a BW warning of increased risk of death related to psychosis and behavioral problems in elderly patients with dementia.[35] (Where have we seen this lately?)

A REMS that generated considerable controversy is the one for the abortion drug mifepristone. The FDA approved mifepristone but concluded that certain restrictions were necessary to ensure its safe use. It received both a BW for rare, but potentially fatal, bleeding episodes, and a REMS.[36] The initial REMS in 2011 required prescribers to be certified. They also needed to demonstrate necessary qualifications to assess whether patients are appropriate candidates for the drug and provide intervention in case of complications. It also restricted dispensing to in-person in a clinic, medical office, or hospital visit. (Notably, the so called "in-person dispensing requirement" was temporarily lifted during the COVID-19 public health emergency, permitting telehealth prescribing.) The FDA determined in 2021 that the REMS should be modified to reduce the burden on the healthcare delivery system and improve access to this time-sensitive medication. The modifications removed the in-person requirement and also permitted pharmacies to become certified to dispense the drug. These changes spawned numerous lawsuits by states and healthcare providers on both sides of this highly contentious issue: one side wanting to reinstate the in-person requirement and the other to eliminate the REMS. Some of these suits are still ongoing.[37]

REMS have also created another controversy. The FDA, the Federal Trade Commission, generic drug manufacturers, and some members of Congress have expressed concern that brand-name manufacturers are using REMS to prevent or delay generic drugs from entering the market. The Director of the CDER, for example, has testified that some brand pharmaceutical companies have used REMS and distribution restrictions to impede competition by withholding or refusing to sell samples of the branded drug to the generic company for purposes of bioequivalence testing and prolonging negotiations related to developing a single, shared system of REMS.[22]

MEDICATION GUIDES

Another means of alerting patients to potential risks is the MG.[38] An MG is part of the FDA-approved prescription drug labeling for certain prescription drugs when the FDA determines that[38]

- Patient labeling could help prevent serious adverse reactions
- The drug has serious risk(s) relative to benefits of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product, or
- Patient adherence to directions for use is crucial to the drug's effectiveness

The medication's manufacturer develops MGs, but the FDA must approve them. They are required to be distributed to the patient or the patient's agent at the time of dispensing in paper form although the patient may request electronic delivery instead.[38]

The MG contains information on proper use of the drug product, such as contraindications, how to use the drug properly (e.g., adhering to dosing instructions and what to do in case of an overdose), adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently, activities to be avoided while taking the drug, risk to special populations, or risk of dependence.[39]

It is important to appreciate that while MGs may be required for drugs with a BW, not every BW triggers an MG.[8] Consequently, many high-risk discussions may not take place. BWs are primarily intended as signals to healthcare providers providing guidance on what clinicians prescribe and how pharmacists should dispense and function, not as direct patient alerts.[8] Their effectiveness in changing behavior has been questioned.[8] Moreover, even the MGs may not achieve their desired result.

A recent study utilizing 449 patients seeking primary care services (18 to 85 years old) analyzed 185 patient Medication Guides.[40] The authors found that the guides averaged almost 2000 words with a mean reading level of 10-11th grade. Only one guide was deemed suitable for readability. None provided summaries or reviews. Moreover, comprehension of the guides was poor, especially among patients with low or marginal literacy. The authors concluded that current MGs are of little value to patients, as they are too complex and difficult to understand especially for individuals with limited literacy.[40] The **SIDEBAR** describes "plain language" communication tips that manufacturers should use to simplify such patient communications.

In May 2023, the FDA published a proposed rule about a new type of FDA-approved patient labeling, known as Patient Medication Information (PMI).[39] The intent of the PMI is to highlight essential information that patients need to know about the prescription drug product, including basic directions on how to use the product.

SIDEBAR: What is Plain Language?

The U.S. Department of Health and Human Services (DHHS) designed Plain Language Guidelines to help communicators present information so that readers can find, understand, and use information quickly. The guidelines emphasize clarity, organization, and audience awareness—principles that are especially important in healthcare, where misunderstanding can have serious consequences.

A central tenet of plain language is **writing for the intended audience**. This means identifying who the readers are, what they already know, and what they need to do with the information. For example, materials written for patients should avoid technical jargon or, when technical terms are necessary, define them clearly. The guidelines encourage writers to anticipate readers' questions and structure content so that answers are easy to locate.

Organization is another key principle. The DHHS recommends placing the most important information first—often referred to as "front-loading." Readers should not have to work through dense paragraphs to find critical instructions or key messages. Effective use of headings, subheadings, and logical flow allows readers to scan documents and quickly identify relevant sections. Bulleted or numbered lists are encouraged when presenting steps, recommendations, or multiple items, as they improve readability and reduce cognitive load.

Word choice plays a significant role in plain language. The guidelines advocate for using common, everyday words instead of complex or unfamiliar terminology. For instance, "use" is preferred over "utilize," and "help" over "facilitate." Writers should keep sentences relatively short and direct. Active voice—sentence structure that clearly identifies who is responsible for an action—makes instructions more actionable and less ambiguous.

Design and formatting are integral to comprehension. Adequate white space, readable fonts, and consistent formatting make documents more approachable. The guidelines suggest avoiding large blocks of text and instead breaking content into manageable chunks. Visual aids—such as tables, charts, or icons—can enhance understanding when used appropriately, but they should complement, not replace, clear writing.

Another important aspect of the DHHS Plain Language Guidelines is **testing and revision**. Reviewing materials with real users whenever possible ensures the content is understandable and useful. Feedback can reveal gaps in clarity or assumptions about reader knowledge that may not be true. Revising based on this input is an essential step in producing effective communication.

Ultimately, the DHHS Plain Language Guidelines are not about "dumbing down" content but about making it accessible and usable. In healthcare and public health contexts, this approach supports better decision-making, improves patient outcomes, and promotes equity by ensuring that information is understandable to people with varying levels of literacy and background knowledge.

PAUSE AND PONDER: What information do you think a PMI should contain to successfully provide adequate warnings to patients?

RECENT DEVELOPMENTS

As noted above, the inclusion of a BW is not necessarily permanent. An important example is the smoking cessation drug varenicline. The drug was approved in 2006. Shortly after its approval, anecdotal reports from popular press and internet sites, post-marketing case reports, and reports to the FDA's Adverse Event Reporting System suggested that some patients prescribed varenicline had experienced suicidal thoughts and aggressive and erratic behavior.[41] The FDA initiated safety reviews in response to these reports and concluded that the drug was associated with adverse psychiatric events.[41] The agency issued a public health advisory in 2008 and mandated a boxed warning in 2009.[43] Subsequently, a large clinical trial of patients with and without psychiatric illness found that the drug was not associated with an increased incidence of clinically significant neuropsychiatric adverse events. The FDA removed the boxed warning in 2016.[42]

FDA has recently lifted the boxed warning on hormone replacement therapy (HRT) drugs, which are commonly used to treat menopause symptoms.[44] The warning was mandated in 2003 based a study of more than 16,000 post-menopausal women receiving conjugated equine estrogens plus medroxyprogesterone.[3,44] The study found an increased risk of breast and endometrial cancers, stroke, blood clots, heart attacks, and dementia associated with the use of the hormone therapy.[3,44] Following the implementation of the label, the use of these treatments among postmenopausal women decreased from 30% to 5% over the next two decades.[3]

FDA removed the BW in November 2025, citing “fear and misinformation surrounding hormone replacement therapy.”[44] The FDA justified the change by noting problems in the initial research, including “the average age of women in the study was 63 years—over a decade past the average age of a woman experiencing menopause—and study participants were given a hormone formulation no longer in common use.”[44] Moreover, randomized studies showed that women who initiate HRT within 10 years of the onset of menopause (generally before age 60) have a reduction in all-cause mortality and bone fractures, and may reduce the risk of cardiovascular disease and Alzheimer’s disease.[45] The FDA’s actions further illustrate the effect that a BW has on prescribing and use and also the dynamic nature of the warnings. Of note, an epidemiologist pointed out that these changes in labeling were not the result of new information but rather a reconsideration and reassessment of the risk-benefit for these drugs.[3] However, FDA is not seeking to remove the boxed warning for endometrial cancer for systemic estrogen-alone products.

PAUSE AND PONDER: How would you have handled the situation presented at the beginning of this activity?

SUMMARY

The FDA has a number of tools that can be used to communicate drug risks to healthcare providers and patients. These include boxed warnings, REMS, and MGs. Pharmacy personnel should be aware of these different tools and how they are developed to manage the risk-benefit of drugs. In addition, pharmacy personnel should recognize that the warnings are subject to change and need to remain aware of the evolving judgment on how risks should be managed. They also need to be ready to answer questions from patients receiving these warnings.

Figure 1. Disseminating Risk Information Appropriately

Best

❶ **Be COMMUNITY CHAMPIONS** and whenever possible, talk about appropriate use of medications for which you must provide risk management materials

❷ **Encourage discussion** with patients about all risk warning documents and walk them through the paperwork when you can

❸ **Collaborate actively with prescribers** to ensure that they know you know the warnings and are an active team member!

Better

❶ **Draft a chart of commonly prescribed medications** used in your practice setting that require Medication Guides

❷ **Remember that boxed warnings** don't necessarily mean a presciber cannot or should not use a medication; it the prescriber and patient need to assess risk/benefit

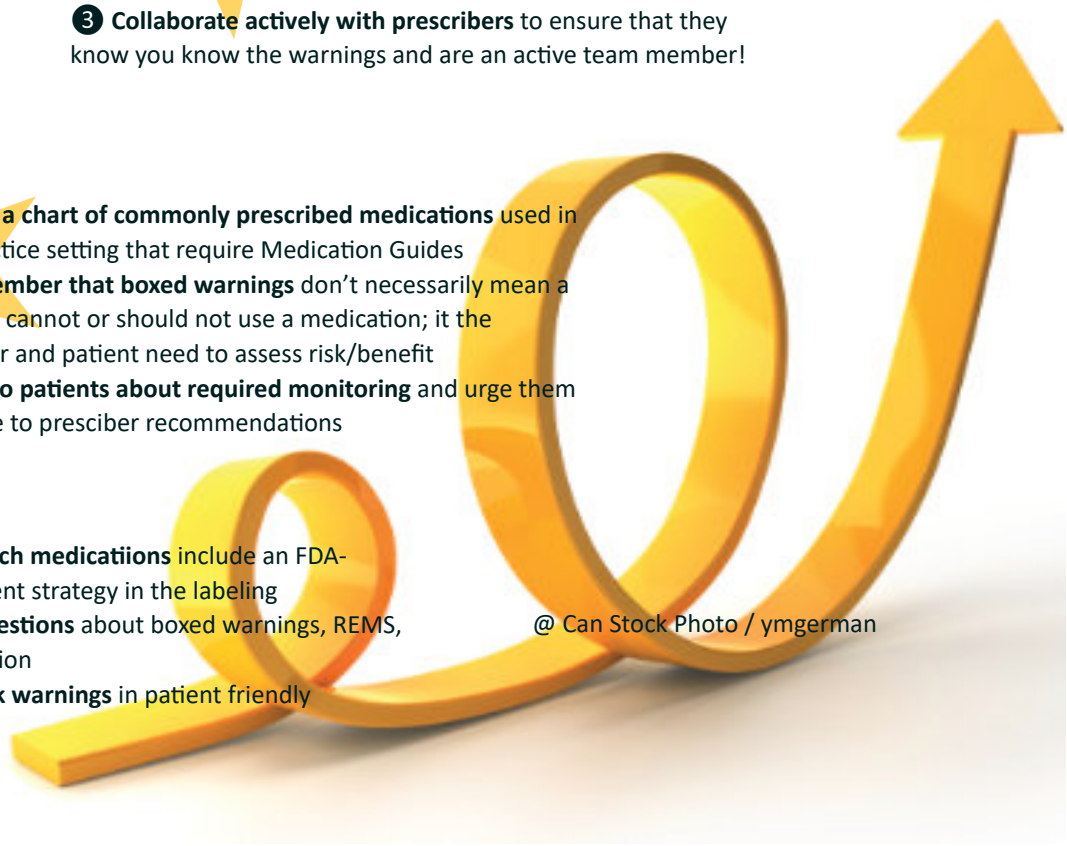
❸ **Talk to patients about required monitoring** and urge them to adhere to presciber recommendations

Good

❶ **Ensure you know which medicatiions** include an FDA-mandated risk management strategy in the labeling

❷ **Anticipate patient questions** about boxed warnings, REMS, and other safety information

❸ **Be able to explain risk warnings** in patient friendly language!



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REFERENCES

1. U.S. Food and Drug Administration. Guidance for Industry. Warnings and Precautions,
Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format. October 2011. Accessed April 9, 2026. https://www.fda.gov/media/71866/download
2. Specific Requirements On Content And Format Of Labeling For Human Prescription Drug And Biological Products Described in § 201.56(b)(1).21 CFR 201.57 Accessed April 9, 2026. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-B/section-201.57
3. Coulson M. What is a Black Box Warning? Johns Hopkins Bloomberg School of Health. Accessed April 9, 2026. https://publichealth.jhu.edu/2025/what-is-a-black-box-warning
4. Mullady RG. Everything You Needed and Wanted to Know About Black Boxed Warnings. VLex January 01, 2001. Accessed April 9, 2026. https://law-journals-books.vlex.com/vid/everything-needed-wanted-boxed-warnings-52940328
5. Smollin CG, Fu J, Levin R. Recognition and Knowledge of Medications with Black Box Warnings Among Pediatricians and Emergency Physicians. *J Med Toxicol*. 2016;12(2):180-184. doi: 10.1007/s13181-015-0519-3.
6. Laurent A. The FDA Boxed Warning: Regulatory Strategy & Negotiation. Intuition Labs. Updated January 25, 2026. Accessed April 9, 2026. https://intuitionlabs.ai/articles/fda-boxed-warning-negotiation
7. U.S. Food and Administration. Prescription Drug Advertising; Content and Format for Labeling of Human Prescription Drugs. *Fed Reg*. 1979;44(124):37434-37467.
8. Dinerstein C. The Black Box: The FDA's Strongest Warning is a Work in Progress. American Council on Science and Health. December 17, 2025. Accessed April 9, 2026. https://www.acsh.org/news/2025/12/17/black-box-fdas-strongest-warning-work-progress-49876
9. Panagiotou OA, Contopoulos-Ioannidis DG, Papanikolaou PN, Ntzani EE, Ioannidis JP. Different black box warning labeling for same-class drugs. *J Gen Intern Med.* 2011;26(6):603-610. doi: 10.1007/s11606-011-1633-9.
10. Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. *Arch Intern Med*. 2010;170(1):96-103. doi: 10.1001/archinternmed.
11. Cheung A, Sacks D, Dewa CS, Pong J, Levitt A. Pediatric prescribing practices and the FDA Black-box warning on antidepressants. *J Dev Behav Pediatr.* 2008;29(3):213-215. doi: 10.1097/DBP.0b013e31817bd7c9.
12. Kramer KJ. The Surprising Re-emergence of Droperidol. *Anesth Prog.* 2020;67(3):125-126. doi: 10.2344/anpr-67-03-14.
13. Perkins J, Ho JD, Vilke GM, DeMers G. American Academy of Emergency Medicine Position Statement: Safety of Droperidol Use in the Emergency Department. *J Emerg Med.* 2015;49(1):91-7. doi: 10.1016/j.jemermed.2014.12.024.
14. 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(17):2215-2220. doi: 10.1001/jama.287.17.2215.
15. Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA.* 2017;317(18):1854–1863. doi:10.1001/jama.2017.5150
16. Schick, A. (2017). Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals. Accessed April 9, 2026. https://link.springer.com/article/10.1007%2Fs40264-017-0526-1
17. U.S. Food and Drug Administration. Drug Therapeutics & Regulation in the U.S. January 31, 2023. Accessed April 9, 2026. https://www.fda.gov/about-fda/fda-history-exhibits/drug-therapeutics-regulation-us
18. Georgi, Andrew T., "The FDA Black Box Warning System: The Utmost in Drug and Patient Safety?" (2010). Yale Medicine Thesis Digital Library. 200. Accessed April 9, 2026. http://elischolar.library.yale.edu/ymtdl/200
19. Wagner AK, Chan KA, Dashevsky I, Raebel MA, Andrade SE, Lafata JE, Davis RL, Gurwitz JH, Soumerai SB, Platt R. FDA drug prescribing warnings: is the black box half empty or half full? *Pharmacoepidemiol Drug Saf.* 2006;15(6):369-86. doi: 10.1002/pds.1193.
20. Barclay L. Inconsistent Adherence to Black Box Warnings: A Newsmaker Interview with Anita Wagner, PharmD, DPH. *Medscape*. November 18, 2005. Accessed April 9, 2026. https://www.medscape.com/viewarticle/517424?form=fpf
21. U.S. Food and Drug Administration. FDA's Role in Managing Medication Risks. January 26, 2018. Accessed April 9, 2026. https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks
22. Sheikh HZ. FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development. Congressional Research Service. March 16, 2018. Accessed April 9, 2026. https://www.congress.gov/crs-product/R44810#fn19
23. Patient Package Inserts for Oral Contraceptives. 21 CFR 310.501. Accessed April 9, 2026. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-310/subpart-E/section-310.501
24. Udkow GP, Lasagna L, Weintraub M, et al. The Safety and Efficacy of the Estrogen Patient Package Insert. A Questionnaire Study. *JAMA*. 1979;242;(6):536-539. doi:10.1001/jama.1979.03300060038025
25. Rowe HM. Patient Package Insert: The Proper Prescription? *Food Drug Law J.* 1995;50(1):95-124.
26. Pharmaceutical Mfrs. Ass'n v. FDA, 484 F. Supp. 1179 (D. Del.), aff d, 634 F.2d 106 (3d Cir. 1980). Accessed April 9, 2026. https://law.justia.com/cases/federal/district-courts/FSupp/484/1179/1431455/
27. U.S. Food and Drug Administration. Frequently Asked Questions (FAQ) About REMS. January 26, 2018. Accessed April 9, 2026. https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems
28. Thaul S. FDA Amendments Act of 2007 (P.L. 110-85). Congressional Research Service. April 27, 2010. Accessed April 9, 2026. https://www.congress.gov/crs-product/RL34465
29. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategies. Updated May 20,2025. Accessed April 9, 2026. https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems

30. U.S. Food and Drug Administration. Roles of Different Participants in REMS. May 7, 2024. Accessed April 9, 2026. https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/roles-different-participants-rems
31. Black L. Accutane and the Evolution of a Warning. Accessed April 9, 2026. https://journalofethics.ama-assn.org/article/accutane-and-evolution-warning/2006-08
32. iPledge. Accessed April 9, 2026. https://ipledgeprogram.com/#Main
33. Gupta N, Gupta M. The Controversies Surrounding Acne and Suicide: Essential Knowledge for Clinicians. *Cureus*. 2023;15(8): e43867. doi: 10.7759/cureus.43867.
34. Weintraub D, Schoen I. The FDA Has Ended Required Blood Monitoring for Clozapine Use—Wi35.ll This Impact the Management of Parkinson's Disease Psychosis? *Movement Disord*. 2025**;** https://doi.org/10.1002/mds.30295Digital Object Identifier (DOI). Accessed April 9, 2026. https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.30295
35. U.S. Food and Drug Information. Information of Clozapine. February 25, 2025. Accessed April 9, 2026. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-clozapine
36. U.S. Food and Drug Administration. Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation. February 2, 2026. Accessed April 9, 2026. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation
37. Expanding Medication Abortion Access. Mifepristone Related Litigation As of January 28, 2025. Accessed April 9, 2026. https://emaaproject.org/wp-content/uploads/2025/01/EMAA-__-Mifepristone-Court-Cases-Updated-01.28.25.docx.pdf
38. U.S. Food and Drug Administration. Patient Labeling Resources. August 19, 2024. Accessed April 9, 2026. https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/patient-labeling-resources
39. CFR 21:208. Accessed April 9, 2026. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-208
40. Wolf MS, King J, Wilson EA, et al. Usability of FDA-approved medication guides. *J Gen Intern Med*. 2012;27(12):1714-1720. doi:10.1007/s11606-012-2068-7
41. Davies NM, Thomas KH. The Food and Drug Administration and varenicline: should risk communication be improved? *Addiction*. 2017;112(4):555-558. doi: 10.1111/add.13592.
42. Desai RJ, Good MM, San-Juan-Rodriguez A, Henriksen A, Cunningham F, Hernandez I, Good CB. Varenicline and Nicotine Replacement Use Associated With US Food and Drug Administration Drug Safety Communications. *JAMA Netw Open*. 2019 Sep 4;2(9):e1910626. doi: 10.1001/jamanetworkopen.2019.10626.
43. Food and Drug Administration (FDA) . Drug Safety Information for Heathcare Professionals > Information for Healthcare Professionals: Varenicline (marketed as Chantix) and Bupropion (marketed as Zyban, Wellbutrin, and generics). 2009. Accessed April 9, 2026. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169986.htm
44. U.S. Food and Drug Administration. HHS Advances Women's Health, Removes Misleading FDA Warnings on Hormone Replacement Therapy. November 10, 2025. Accessed April 9, 2026. https://www.fda.gov/news-events/press-announcements/hhs-advances-womens-health-removes-misleading-fda-warnings-hormone-replacement-therapy
45. Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2002;288(3):321–333. doi:10.1001/jama.288.3.321