

Clinical Considerations of Risk Evaluation and Mitigation Strategies in Health Care Systems



Demystifying Risk Evaluation and Mitigation Strategies:

Medication Guide Distribution Requirements and Standardization

The Food and Drug Administration Amendments Act (FDAAA) of 2007 granted the FDA new authorities to require risk evaluation and mitigation strategies (REMS) to manage the risks associated with a drug.¹ Although medication guides can be part of a REMS or developed separately, they are the most common component of REMS. Other possible components of REMS include communication plans, elements to assure safe use (e.g., special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, patient registries), and implementation systems, although some REMS comprise only a medication guide. Between March 25, 2008, when the REMS provisions of FDAAA took effect and January 1, 2011, FDA approved more than 150 medication guides as part of REMS, including 108 medication guide-only REMS.²

Medication Guide Distribution in Various Care Settings

Medication guides are the most common component of REMS. Some health care professionals have had questions regarding distribution of medication guides when a drug is dispensed to a health care professional who administers it to the patient in an inpatient setting or outpatient clinic (e.g., clinic, dialysis or infusion



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center). Clarification on this important issue arrived on February 28, 2011, when FDA issued a draft guidance for industry on medication guides that describes situations in which a medication guide need not be distributed. The Agency “intends to exercise enforcement discretion concerning distribution of a medication guide to a patient.”²

The table below summarizes requirements for distribution of medication guides according to setting. In all settings, including the inpatient environment, distribution of a medication guide is required when the patient or his or her agent requests one. The request of a medication guide by a patient or his or her agent is the only requirement for inpatients mentioned in the guidance. In the outpatient setting, when a drug is dispensed to a health care professional for administration to a patient (e.g., clinic, infusion center) a medication guide must be provided the first time the drug is dispensed as well as whenever the medication guide is materially changed. The goal of relaxing these requirements is to continue to protect patients from harm without unduly burdening the health care system.

While the information on medication guide distribution in the draft guidance was of particular interest and practical importance to health care professionals, it also included information on how manufacturers and FDA can interact to maintain medication guides. As described above, medication guides can be part of a REMS or a separate labeling requirement for a product

that does not have a REMS. The February 2011 draft guidance for industry on medication guides includes a proposed procedure for drug manufacturers to request removal of medication guides from REMS (or elimination of medication guide-only REMS). If the manufacturer does not believe that the medication guide is needed to ensure that the benefits of the drug outweigh the risks, the proposed procedure can be followed.² The medication guide could remain part of the FDA-approved product labeling, even if it is removed from the REMS or the REMS is eliminated. To completely eliminate a medication guide, a manufacturer would need to formally request that the medication guide be removed from the approved product labeling.

The FDA accepted public comments about the draft guidance until May 31, 2011. ASHP submitted comments to the agency on May 19, 2011 mostly in support of the draft guidance. ASHP concurred with FDA that a medication guide need not be given in the inpatient setting unless requested by the patient or his or her agent. Also, ASHP agreed that for drugs administered by health care professionals in the outpatient setting that medication guides need only be provided (1) at the time of first administration, (2) when the medication guide materially changes, or (3) at the patient’s request. Health care professionals can use information in the draft guidance when implementing their medication guide distribution practices but should be on the lookout for the final guidance from FDA.

Table. FDA Proposed Medication Guide Enforcement Discretion Policy²

Setting	Patient or Patient’s Agent Requests Medication Guide	Medication Guide Distributed Each Time Drug Dispensed	Medication Guide Distributed At Time of First Dispensing	Medication Guide Distributed When Medication Guide Materially Changed
Inpatient	Must dispense medication guide	Not necessary to dispense medication guide*	Not necessary to dispense medication guide*	Not necessary to dispense medication guide*
Outpatient when dispensed to health care professional for administration to patient (e.g., clinic, infusion center)	Must dispense medication guide	Not necessary to dispense medication guide*	Must dispense medication guide	Must dispense medication guide
Outpatient when dispensed directly to patient or caregiver (e.g., retail pharmacy, hospital ambulatory pharmacy)	Must dispense medication guide	Must dispense medication guide	Must dispense medication guide	Must dispense medication guide

FDA = Food and Drug Administration

*Technical terms in guidance are “FDA intends to exercise enforcement discretion; medication guide need not be dispensed.”

Progress toward REMS Standardization

Reauthorization of the Prescription Drug and User Fee Act (PDUFA), legislation that authorizes FDA to collect fees from drug manufacturers and expedites the drug approval process, is required every 5 years. The legislation has been reauthorized three times since 1992.³ The need to reauthorize PDUFA III served as the primary impetus for passage of the FDAAA in 2007. The current version, known as PDUFA IV, is set to expire in September 2012. The reauthorization process has already begun. Last year the FDA convened a public meeting to discuss PDUFA. Input from stakeholders, including ASHP, was solicited. The need for standardization of REMS was among the issues raised by ASHP in conjunction with discussions of PDUFA renewal.

In response to requests from stakeholders, development of standardized REMS that can be incorporated into existing health care systems was among various FDA plans described in late 2010.⁴ The goal of standardization is to minimize the workload and burden on health systems associated with REMS requirements. Manufacturers are responsible for submitting a proposed REMS prior to approval of a drug product.⁵ The FDA issued a draft guidance on REMS in 2009 to guide manufacturers in preparing proposed REMS.⁶ In this draft guidance, FDA specifically requested that manufacturers include in the supporting documents that accompany their REMS submissions information regarding relevant past experiences to assist in the development of REMS that are compatible with established distribution, procurement, and dispensing systems within the health care delivery system and that avoid the cost of implementing REMS tools already determined to be unsuccessful.⁶ Manufacturers were encouraged to provide applicable information or evaluations from past experiences with products or programs that are similar to the proposed REMS. Descriptions of the available evidence regarding the effectiveness of each element and tool were requested in the proposed REMS.

An example of progress toward REMS standardization is Abstral[®], an immediate-release fentanyl transmucosal tablet used to manage breakthrough pain in adults with cancer.^{7,8} The goals of the REMS are to ensure that the drug is dispensed only to opioid-tolerant patients, prevent inappropriate conversion between fentanyl products, avoid accidental use of the drug by children and other persons for whom it was not prescribed, and educate prescribers, pharmacists, and patients about the potential for misuse, abuse, addiction, and

overdose. The REMS comprises a medication guide and elements to assure safe use, with certification of outpatient prescribers and inpatient and outpatient pharmacies and enrollment programs for distributors and patients. Key components of the REMS that have been standardized for use with any immediate-release fentanyl transmucosal tablet product include the REMS document, a patient-prescriber agreement, and an enrollment form.

Extended-Release and Long-Acting Opioid Analgesics

On April 19, 2011, plans for new REMS requirements for extended-release and long-acting opioid analgesics were announced by FDA and the White House Office of National Drug Control Policy as part of Epidemic: Responding to America's Prescription Drug Abuse Crisis, a comprehensive action plan to address the problem of prescription drug abuse in the United States.^{9,10} Components of the plan include:

- ❑ Prescriber education about the risks and benefits of opioid analgesics, patient selection, proper pain management, monitoring of therapy, patient counseling, and detection of misuse, abuse, and addiction;
- ❑ Distribution of medication guides to patients and provision of patient education about the risks and benefits of opioid analgesic use and proper medication use, storage, and disposal;
- ❑ Safe, convenient, and environmentally-responsible disposal that prevents medications from getting into the wrong hands; and
- ❑ Law enforcement (expansion of state-based prescription drug monitoring programs, other efforts to reduce the number of "pill mills" and doctor shopping).

Extended-release and long-acting opioid products are the focus of the REMS because of the greater risks of serious side effects, overdose, and death associated with misuse and abuse of these products compared with immediate-release products.¹⁰ Preventing harm from extended-release and long-acting opioid products without limiting access for patients with a legitimate need for the products is the goal of the REMS. The FDA plans to monitor patient access to opioid analgesics to ensure that it is not compromised.

The FDA has notified manufacturers of extended-release and long-acting opioid analgesics that they must submit REMS proposals within 120 days.⁹ The agency expects the manufacturers to collaborate in developing educational materials for use in a class-wide single shared sys-

tem to reduce the burden on the health care system.¹⁰ The REMS provisions are expected to be implemented by early 2012. Prescriber education may be administered directly by manufacturers or through accredited continuing medical education providers. Manufacturers will be required to establish goals for and monitor the percentage of prescribers who have completed educational programs at specific times. A list of extended-release and long-acting opioid products with REMS requirements is available online (<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm>).

In a July 2010 joint meeting of two FDA advisory committees convened to discuss a class REMS for extended-release and long-acting opioid analgesics, mandatory prescriber education linked to prescriber registration

with the Drug Enforcement Administration (DEA) was suggested.¹⁰ However, the current plan is for the education system for prescribers to be voluntary with no link to the DEA registration system because of concerns about an adverse effect on patient access to opioid analgesics and the potential burden on the health system. There are no plans to establish a separate system for registering prescribers of extended-release and long-acting opioid analgesics because it would duplicate the DEA registration system. Prescriber education may become a condition for obtaining DEA registration in the future.

ASHP Advantage in partnership with the Society of Hospital Medicine recently embarked on a timely educational initiative for pharmacists and physicians interested in current regulatory considerations relating to ensuring the safety of medications. The initiative is supported by an educational grant from Astellas Pharma Global Development, Inc. Educational activities, in various formats, are available. For complete program information visit the initiative portal at www.remsupdates.org.

References

1. U.S. Food and Drug Administration. Sec. 505-1. [21 USC §355-1] Risk evaluation and mitigation strategies. February 2008, updated April 30, 2009. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm109090.htm> (accessed 2011 Aug 15).
2. U.S. Food and Drug Administration. Draft guidance for industry on medication guides—distribution requirements and inclusion of medication guides in risk evaluation and mitigation strategies; availability. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf> (accessed 2011 Aug 15).
3. U.S. Food and Drug Administration. Prescription Drug User Fee Act (PDUFA). <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm> (accessed 2011 Aug 15).
4. Woodcock J. Update from CDER. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM239634.pdf> (accessed 2011 Aug 15).
5. 110th U.S. Congress. Food and Drug Administration Amendments Act of 2007. September 27, 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110 (accessed 2011 Aug 15).
6. U.S. Food and Drug Administration. Draft guidance for industry: format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications. September 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> (accessed 2011 Aug 15).
7. U.S. Food and Drug Administration. FDA approves opioid analgesic to help cancer patients manage pain. January 7, 2011. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239490.htm> (accessed 2011 Aug 15).
8. Traynor K. First standardized REMS approved. *Am J Health Syst Pharm.* 2011; 68:366-8.
9. U.S. Food and Drug Administration. FDA acts to reduce harm from opioid drugs. April 19, 2011. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm251830.htm> (accessed 2011 Aug 15).
10. U.S. Food and Drug Administration. Questions and answers: FDA requires a risk evaluation and mitigation strategy (REMS) for long-acting and extended-release opioids. April 19, 2011. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251752.htm> (accessed 2011 Aug 15).