

Louisiana Drug Utilization Review Education

Review of FDA Risk Evaluation and Mitigation Strategy (REMS)

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In 2007, Congress approved the Food and Drug Administration Amendments Act (FDAAA) which gave the FDA new authority over the regulation of drugs and drug marketing requirements. A provision in this legislation was titled the Risk Evaluation and Mitigation Strategy (REMS) for medications that may be associated with higher safety risks to the public. The REMS program was designed to better ensure appropriate and safe use of medications. The FDA would now have the power to control marketing and clinical studies prior to drug approval, and to increase public awareness of drug study data.

The FDA has the authority to determine which medications (or therapeutic classes of medications) need to include a REMS. This is true not only for new medications, but also for medications that have already been FDA-approved. If a new safety warning is issued or if a serious adverse event is seen in post-marketing surveillance, a request for a REMS may be triggered by the FDA for that particular medication or therapeutic class. Post-marketing surveillance identifies problems that were not seen prior to a medication's approval, usually due to relatively small sample sizes in clinical trials. Commonly used tools to identify these problems include the Adverse Event Reporting System (AERS) and MedWatch.²

One element of the FDAAA allows the marketing of medications that otherwise may not have gained approval due to a known, potentially serious adverse event. In this scenario, the FDA may require that a medication include "Elements to Assure Safe Use" or ETASU.⁴ Many ETASU involve health-care provider certification, meaning physicians who prescribe a high-risk medication will have to receive specialty training prior to prescribing. Once a REMS is requested by the FDA, the document must contain certain elements: product name, drug class, contact information for those responsible for the REMS policy, one or more overall goals, list of specific REMS elements, implementation system, and timetable for assessment submissions.¹

There are several factors that determine whether a medication will require a REMS. These include: ³

1. Size of population studied
2. Seriousness of disease
3. Expected benefit and duration of treatment
4. Any known serious adverse events
5. Any new molecular entity

Once a REMS is required by the FDA, the drug manufacturer must provide the data requested within the REMS and submit its findings to the FDA.

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Currently, there are several FDA-approved REMS that drug manufacturers can use, and each one was designed to increase both patients' and practitioners' awareness of a medication's potential adverse effects. However, there are potential limitations with each of them as well. The existing REMS for medications may include:²

1. Medication Guides (MedGuides)
2. Informed consent
3. Mandatory lab monitoring
4. Restricted distribution
5. Specialty training
6. Specific ordering/inventory process
7. Patient registries
8. Prescription stickers

MedGuides are a common element of REMS, and may include a "Dear Doctor" letter. Though MedGuides are written for patients, some patients feel as if they are hard to understand because they sometimes contain lengthy technical information and are written at a high reading level. Also, the MedGuides may create potential burdens for the healthcare providers by increasing workload with additional paperwork. The sheer number of medications that have MedGuides can be very time consuming for the pharmacist at the time of dispensing. There are currently over 100 different medications and therapeutic classes of medications that require MedGuides at the time of dispensing.² Mandatory lab monitoring is used for certain medications such as clozapine that can cause serious adverse events, which can be prevented by discontinuing the medication at the first sign of altered lab values. Both specialty training and restricted distribution pose their own problems, most noticeably in rural areas, where access to certain medications may be limited and care for the patient may be delayed. For example, a patient on a medication that can be prescribed only by a physician who has completed training on that medication is admitted to a rural hospital; the facility may not have an approved physician to administer that medication and the patient may go days without receiving it.

REMS for opioid analgesics were set to be reviewed by the FDA in October 2010; however, a report in *Medscape Medical News* stated that the FDA had decided to delay the review until 2011.⁵ The opioid REMS would stand to dramatically change the prescribing of this class of medications which could have a major impact on both physicians and patients. Two major issues were at the forefront of the FDA's decision for the delay: the question of whether or not to include all opiate formulations rather than the original FDA recommendation of only the extended-release or long-acting opiates, and the debate concerning the need for increased training of safe and effective opioid prescribing for physicians. The first became an issue when the FDA advisory committee proposed that the REMS cover all opiates, but the assumption was that physicians would be less likely to prescribe short-acting medications for acute pain if there was an increase in requirements to do so.⁵ The second issue arose after debate over whether increased physician education regarding the prescribing of opiates should be voluntary or mandatory. If this became an addition to the Drug Enforcement Agency opiate prescribing requirements, it would not only have to be approved by Congress, but the committee's fear was that many physicians would choose not to prescribe opiates to avoid the inconvenience of the additional requirements.⁵

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REMS is a post-marketing surveillance process created by the FDA to help ensure the safety of medications and to help improve communication between pharmaceutical companies, prescribers, and patients. The goal is to help improve patient safety and minimize potential drug-related issues. Hopefully, the collaborative efforts of the FDA and healthcare providers will maximize the benefit of REMS and minimize the potential pitfalls of a medication's adverse effects.

Table 1: Examples of Common Medications with Approved REMS*

Drug Name	Date REMS Approved	REMS Components (All REMS include timetable for assessment)
Actos (pioglitazone hydrochloride) Tablets	9/9/2009	Medication guide
Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder)	4/30/2008	Medication guide
Aranesp (darbepoetin alfa) Injection	2/16/2010	Medication guide, communication, elements to assure safe use, implementation system
Byetta (exanatide) Injection	10/30/2009	Medication guide, communication plan
Chantix (varenicline) Tablets	10/19/2009; modified 4/22/2010	Medication guide
Effient (prasugrel) Tablets	7/10/2009; 4/16/2010	Medication guide, communication plan
Levaquin (levofloxacin) Tablets, Injection, and Oral Solution	4/27/2009	Medication guide
Reglan (metoclopramide hydrochloride) Tablets	9/4/2009	Medication guide
Tracleer (bosentan) Tablets	8/7/2009; modified 2/19/2010	Medication guide, elements to assure safe use, implementation system
Victoza (liraglutide) Injection	1/25/2010	Medication guide, communication plan

*For a complete list, please refer to the FDA website:

www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

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