An Overview of Risk Evaluation and Mitigation Strategy (REMS): Elements Related to Medication Use and Dispensing

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This is a knowledge-based activity.  
See end of article for CE details.

Target Audience: Pharmacists  
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Goal: To provide an overview of the FDA REMS program and issues related to medication dispensing and use.

Objectives: At the conclusion of this lesson, successful participants should be able to:
1. Describe the history of the FDA REMS program and issues surrounding implementation.  
2. Review the components and requirements for the various REMS plans.  
3. Discuss recent updates in the REMS purview of opioid drug products.

INTRODUCTION

While medications can help cure diseases and improve quality of life, they also cause adverse effects that range from disruptive to potentially life-threatening. The United States Food and Drug Administration (FDA) and manufacturers are aware of many adverse effects associated with medications during drug development, while others may not present until more widespread patient exposure and post-marketing experience. To allow for higher risk medications to be brought to market and available for patient use in an expedited manner, the FDA Amendments Act of 2007 permitted the FDA to implement the Risk Evaluation and Mitigation Strategy (REMS). This risk management program provides FDA with the authority to require post-marketing surveillance for prescription medications and the structure for manufacturers to ensure that the benefits of their products outweigh the risks. The REMS program may be appropriate for new drugs and biologics as well as those previously introduced to the market. As of May 2012, approximately 100 prescription medications fall under the REMS program and the majority of new products approved in the last year had some element of REMS requirements.

REMS COMPONENTS AND REQUIREMENTS

For medications selected for REMS purview, manufacturers are required to design a plan intended to help mitigate potential harmful effects. Each FDA-approved REMS plan has specific components and requirements that vary depending on the severity of the drug’s risk, the population exposed, and the distribution or administration setting. REMS components may include Medication Guides, communication plans for health care providers, elements to assure safe use (ETASU), and a specified implementation system (Table 1).

One or more components of the REMS program may apply for a particular medication at any stage of the product marketing. For example, the ESA APPRISE Oncology Program (epoetin alfa, darbepoetin alfa) currently requires a medication guide, communication plan, ETASU and implementation system, whereas the isotretinoin iPLEDGE Program requires a medication guide, ETASU and implementation system, but no formal communication plan. Rosiglitazone (Avandia®), with no requirements for supplementary post-market surveillance at market entry, now falls under several components of REMS.

Medication Guides

Medication Guides are written in layman’s terms with the goal of providing patient information for prescription drugs and biologics that the FDA determines have the potential to pose serious and significant public health concern. While the FDA definition of a Medication Guide and a package insert are very similar, in contrast, package inserts are available for all FDA-approved drugs and provide more limited information regarding use of the drug. Medication Guides are the most common REMS provision.

The FDA may require a Medication Guide for a drug product under the following circumstances:
- Patient labeling could help prevent serious adverse effects.
- There are serious risks (relative to benefits) about which patients should be made aware because this information could affect the decision to use or continue use of the product.
The product is important to health and patient adherence to directions for use is crucial to effectiveness.

Manufacturers of drug products for which a Medication Guide is required must ensure that a sufficient number are supplied or provide the means for access to distributors, packers, and authorized dispensers. The requirements for providing a Medication Guide to the patient or their agent vary depending on the drug distribution or administration setting. When a drug is dispensed directly to the patient or caregiver in an outpatient setting (e.g. retail pharmacy, hospital ambulatory pharmacy, clinic providing samples), a Medication Guide is required each time the drug is dispensed. In an outpatient setting when the drug is dispensed to a health care professional for administration to the patient (e.g. clinic, dialysis or infusion center), a Medication Guide is required with the first administration of the drug (not each time), when the Medication Guide is materially changed, if there are specific ETASU requirements, or upon patient request. A Medication Guide is only required in the inpatient setting (e.g. hospital, nursing home) if requested by the patient or their agent or if the drug requires ETASU with specific requirements.

The majority of drug products approved in 2012 have a required Medication Guide. Common medications requiring a Medication Guide include pioglitazone (Actos®), oxycodone controlled-release tablets (Oxycotin®), varenicline (Chantix®), bupropion (Wellbutrin XL™), and venlafaxine (Effexor®), among others.

Communication Plans1,5 Communication plans are FDA-approved tools to support REMS implementation and inform providers about the serious risks of drug products and required or suggested safety protocols. Per FDA approval, information may be disseminated through various venues, including direct mailings (“Dear Health Care Provider”), print advertising, and professional organizations and meetings (e.g. educational information through speakers, medical science liaisons). Medications requiring a communication plan include liraglutide (Victoza®), quinine sulfate (Qualaquin®), rivaroxaban (Xarelto®), tigacrelor (Brilinta™), and fluticasone/salmeterol (Advair Diskus®).

Elements to Assure Safe Use (ETASU)1,5 ETASU program requirements provide the most extensive oversight and help ensure safe access to medications with more serious risks. Under the REMS purview, ETASU requirements may apply to the health care provider, the patient, or both. Elements required may include enrollment in registry programs, focused training or certification, drug administration in limited settings (e.g. hospitals), Medication Guides, documentation of safe use conditions, or specific patient monitoring. Examples of medications requiring ETASU include rosiglitazone (Avandia®), eptopin alfa (Epogen®/Procrit®), emtricitabine/tenofovir disoproxil fumarate (Truvada®), doxefilide (Tikosyn®), and olanzapine (Zyprexa® Relprevv™).

Implementation System3,5 Certain drug products may also require a specified implementation system for distribution, dispensing, or otherwise meeting REMS requirements. Through such system, the sponsor company may be expected to monitor and evaluate REMS requirement implementation by health care providers and others. Implementation system requirements may include ensuring wholesalers are distributing drug products only to certified or otherwise designated pharmacies, practitioners, or health care settings. Review of participant records may be required to verify appropriate dispensing or administering and meeting all the REMS requirements. Periodic audits of all certified entities may be conducted to ensure compliance with ETASUs and maintaining a validated and secure database may be required for tracking certifications. The FDA may also expect manufacturers to frequently make changes to the implementation system and plan.

REMKS AND OPIOID DRUG PRODUCTS1,7,8 Opioids are clearly an important class of medications for the relief of pain, however are frequently associated with issues of intentional and unintentional misuse, addiction, overdose, and death. To address these issues and facilitate the safe use and prescribing of these medications, the FDA approved a REMS for extended-release (ER) and long-acting (LA) opioids on July 9, 2012. This program is designed to inform both health care providers and patients through a process of continuing education. Information for prescribers will include guidelines for appropriate patient selection and monitoring and counseling patients on the safe use of these medications. Additionally, patients are to receive Medication Guides and other educational materials. Long-acting and extended-release opioids drugs included under this REMS program are methadone (Dolophine®), all morphines (MS Contin®, Kadian®, Avinza®, Embeda®, Oramorph®), oxycodone (OxyConti®, hydromorphone (Exalgan™), transdermal fentanyl (Duragesic®), transdermal buprenorphine (Butrans®), tapentadol (Nucynta® ER) and oxymorphone (Opana® ER). Expected to begin March 2013, opioid manufacturers are required to develop educational materials, provide training to prescribers, and perform periodic assessments of the implementation of the REMS program. Legislative changes will have to occur before prescribers are required to participate in training or have preconditions to prescribing.

For transmucosal immediate-release fentanyl (TIRF) products, the FDA approved the TIRF REMS Access program in December 2011. This single shared REMS plan allows providers to enroll into one system, instead of requiring registration for each individual product. TIRF medicines include fentanyl sublingual tablet (Abstral®), fentanyl citrate oral transmucosal...
lozenge (Actiq®) and its generic equivalents, fentanyl citrate buccal tablet (Fentora®), fentanyl nasal spray (Lazanda®), and fentanyl buccal soluble film (Onsolis™) and fentanyl sublingual spray (Subsys™).

All prescribers of TIRF products intended for use in an outpatient setting or for long-term care and hospice patients who obtain their medications from outpatient pharmacies must enroll in the TIRF REMS Access program. Prescribers of TIRF products only for inpatient use will not be required to enroll. The primary goals of this new shared system are to ensure only opioid-tolerant patients have access to TIRF, prevent inappropriate conversion between fentanyl products, prevent accidental overdose, mitigate the risk of misuse and abuse, and educate providers and patients.

REMS PROGRAM IMPLEMENTATION

Many very commonly used medications fall under REMS review, however most health care providers are not aware of and do not fully understand the REMS program or requirements. A recent survey conducted among Mississippi pharmacists and trainees (N=142) highlights these issues. The survey was designed to evaluate the knowledge of and implementation of REMS among health care providers in our state. Per survey responses, only 37% of pharmacy participants had implemented REMS requirements in their practice setting, though 78% reported that they were at least somewhat familiar with REMS. Most (98%) reported to understand that REMS is a program overseen by the FDA but had limited knowledge of Medication Guide requirements. The majority of students (73%) incorrectly indicated that a Medication Guide should be distributed to a patient each time a drug or biologic is administered (in any setting), compared to 44% of pharmacists. The majority of pharmacists (61%) were interested in receiving more information about REMS (provided as an educational handout after survey completion). In contrast, less than half of students (46%) were interested in the educational information though survey responses indicated that they were less familiar with REMS overall than pharmacists.

There remains a need to increase the overall knowledge and awareness of REMS among health care providers. While the advantages of the REMS program are apparent, there are burdens and disadvantages to the process and implementation (Table 2). The different elements of REMS, necessary certifications and registrations, and requirements for patient education with particular drug products are not universally understood.

Previously there has been little consensus between FDA and other groups as to which drug products should fall under REMS purview. The growing number of REMS programs creates issues that impact workflow and management. There has been limited collaboration among providers on the coordination of REMS requirements across the continuum of patient care. Because of the effort involved and the lack of knowledge and standardization, these measures have not been adopted into general clinical practice. There is also no FDA monitoring of REMS adherence except for particular drug products, most frequently those requiring ETASU. In the future, the FDA will implement increased monitoring and ramifications or sanctions for the lack of REMS participation or adherence at multiple levels. For manufacturers, failure to comply with REMS can result in substantial penalties, ranging from $250,000 per violation and $1 to $10 million per proceeding. As with the TIRF REMS Access program, the FDA is now working with health care providers and others to collaborate and create new solutions and models to avoid confusion and alleviate burdens.

CONCLUSION

The REMS program allows patients to have access to and benefit from crucial therapies which otherwise may not be available. It will become increasingly important that all health care providers play a vital role and work together in REMS participation and adherence. Through following recommendations, providing patient counseling, monitoring efforts, and advocating for changes to improve the REMS program, we can all help ensure that the program objectives are met and patient safety is increased.

REFERENCES


Table 1. REMS Components²

<table>
<thead>
<tr>
<th>Medication Guide</th>
<th>Communication Plan</th>
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<tbody>
<tr>
<td>ETASU</td>
<td>Implementation System</td>
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Table 2. Advantages and Disadvantages of REMS Requirements³

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Promote safe and appropriate use of drugs</td>
<td>• Lack of standardization</td>
</tr>
<tr>
<td>• Provide opportunities for systematic and ongoing data collection, reporting, and feedback on medication safety</td>
<td>• Potential for confusion regarding responsibilities among health care practitioners</td>
</tr>
<tr>
<td>• Allow drugs to be approved that would not otherwise have reached the market because of risks</td>
<td>• Time-consuming, labor intensive and potential for disruption in continuity of care</td>
</tr>
<tr>
<td>• Allow drugs that might have been withdrawn from the market because of risks to remain available to patients</td>
<td>• Lack of reimbursement for extra work involved</td>
</tr>
<tr>
<td>• Provide opportunities for expanded clinical and leadership roles and collaboration among pharmacists, physicians, and other health care practitioners</td>
<td>• Insufficient health care practitioner input to FDA in premarketing development of REMS</td>
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</table>
**Test name:** 2012 Article #9: An Overview of Risk Evaluation and Mitigation Strategy (REMS)

**This test is worth:** 10 points

Select multiple choice answers with a cross or tick:

- Only select one answer
- Select multiple answers

**INSTRUCTIONS:** This page is intended to help participants REVIEW the quiz questions prior to submitting their answers online. Please take the quiz online using the link in the MEMBERS section of the website.

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**Question 1 of 19**

REMS is administered by the:

- **A)** United States Department of Agriculture (USDA)
- **B)** Federal Trade Commission (FTC)
- **C)** U.S. Food and Drug Administration (FDA)
- **D)** Drug Enforcement Administration (DEA)

**Question 2 of 19**

For new medications, the FDA determines whether or not REMS is necessary to:

- **A)** Expedite drug approval
- **B)** Ensure a medication's benefits outweigh its risks
- **C)** Ensure product efficacy during the post-marketing period
- **D)** All of the above

**Question 3 of 19**

The REMS program allows patients to have access to potentially serious risk medications, which might otherwise not ever have been approved to market.

- **A)** True
- **B)** False

**Question 4 of 19**

Over-the-counter products are included under the REMS program.

- **A)** True
- **B)** False

**Question 5 of 19**

REMS requirements for particular medications may include:
Question 6 of 19
A Medication Guide is the same as a package insert.

A) True
B) False

Question 7 of 19
A Medication Guide is required by the FDA when:

A) Any new drug product is approved
B) Product information could help prevent serious adverse events
C) Patients adherence to directions for use is crucial to the drug's effectiveness
D) Both B and C

Question 8 of 19
REMS requires that a Medication Guide be distributed to a patient or their agent:

A) Each time a drug or biologic is administered in any setting
B) Each time a drug or biologic is dispensed directly to a patient or their agent in an outpatient setting
C) With specific ETASU requirements when administered in an inpatient setting
D) All of the Above
E) B and C only

Question 9 of 19
Per REMS requirements, communication plans may inform health care providers about serious risks of drugs through direct mailings and professional education meetings.

A) True
B) False

Question 10 of 19
Through the TIRF REMS Access program, providers must enroll if they prescribe TIRF products intended for use only in the:

A) Outpatient setting
B) Inpatient setting
Question 11 of 19

Did the article help you achieve EACH of the stated objectives? If not, describe in the comment box at the end of this section. Refer to the article for the list of learning objectives.

☐ A) Yes
☐ B) No

Question 12 of 19

Quality of the written material/content?

☐ A) Very Good Quality
☐ B) Good Quality
☐ C) Neutral
☐ D) Poor Quality
☐ E) Very Poor Quality

Question 13 of 19

Overall evaluation of this article?

☐ A) Very Good
☐ B) Good
☐ C) Neutral
☐ D) Poor
☐ E) Very Poor

Question 14 of 19

How much time was required to complete this article?

☐ A) 0.5 hours
☐ B) 1.0 hours
☐ C) 1.5 hours
☐ D) 2.0 hours
☐ E) 2.5 hours

Question 15 of 19

The learning activities (e.g. case studies, quiz) were effective?

☐ A) Strongly Agree
☐ B) Agree
☐ C) Neutral
Question 16 of 19
The information in this article will help assist and reinforce my practice/treatment habits?

- A) Strongly Agree
- B) Agree
- C) Neutral
- D) Disagree
- E) Strongly Disagree

Question 17 of 19
The author(s) did NOT appear to be promoting a product or company? Please use COMMENT box at end of evaluation to explain or provide comment.

- A) Strongly Agree
- B) Agree
- C) Neutral
- D) Disagree
- E) Strongly Disagree

Question 18 of 19
Author(s) communicated material clearly?

- A) Strongly Agree
- B) Agree
- C) Neutral
- D) Disagree
- E) Strongly Disagree

Question 19 of 19
Comments. Please use this space to provide comments related to any of the above questions.
If NO COMMENT, please write *NONE* in the box below.