

## **FDA Background Package**

**For Meeting of Drug Safety and Risk Management (DSaRM)  
and  
Dermatologic and Ophthalmic Drugs Advisory Committees  
(DODAC)**

**Afternoon Session: General REMS Discussion**

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**December 1, 2011**

## **Disclaimer Statement**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the discussion of the evaluation of one of the Risk Evaluation and Mitigation Strategies (REMS) and a general discussion of the evaluation of REMS to the advisory committee as required by the Food and Drug Administration Amendments Act (FDAAA) to gain the Committee's insights and opinions. The background package may not include all issues relevant to the evaluation of REMS and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

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**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**Office of Medication Error Prevention and Risk Management**  
**M E M O R A N D U M**

DATE: November 2, 2011

FROM: Claudia Karwoski, PharmD  
Director  
Division of Risk Management  
Office of Surveillance and Epidemiology, CDER, FDA

TO: Chair, Members and Invited Guests  
Drug Safety and Risk Management Advisory Committee (DSaRM)  
Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)

RE: Overview of the December 1, 2011 DSaRM and DODAC meeting to discuss the evaluation of REMS.

The Food and Drug Administration Amendments Act (FDAAA) requires the Agency to bring, at least annually, one or more drugs with Risk Evaluation and Mitigation Strategies (REMS) with elements to assure safe use (ETASU) before its Drug Safety and Risk Management Advisory Committee (DSaRM) to solicit their views on whether the elements:

1. assure safe use of the drug
2. are not unduly burdensome on patient access to the drug
3. to the extent practicable, minimize the burden on the healthcare delivery system.

To meet that requirement, this joint meeting of the DSaRM and DODAC will consist of a two-part discussion. Each session will include a number of presentations, an open public hearing and a discussion period.

The afternoon session will be a general discussion of how REMS programs may be implemented to minimize the negative effects on patient access to drugs covered by REMS and to decrease the burdens of REMS on the healthcare system. This session will not include any drug-specific information or discussion, but will instead encompass all drugs with REMS that include ETASU.

The following non-voting points to consider will be discussed by the committee members:

**Draft Points to Consider for the Committee: PM session**

1. Discuss and prioritize solutions for challenges regarding integration of REMS into healthcare systems.
2. Discuss analyses and metrics to consider when assessing the effects of REMS with ETASU on
  - a. Safe use of the drug of interest
  - b. Patient care
  - c. The healthcare delivery system

This meeting represents the first opportunity for FDA to seek expert advice regarding these important programs. We are grateful for your participation and thank you for your assistance in providing your expertise and insights to us.

## **2 BACKGROUND**

### **2.1 Objective of afternoon session**

The Food and Drug Administration Amendments Act (FDAAA) of 2007 requires FDA to bring, at least annually, one or more drugs with Risk Evaluation and Mitigation Strategies (REMS) with elements to assure safe use (ETASU) before its Drug Safety and Risk Management Advisory Committee (DSaRM). The DSaRM and the Dermatologic and Ophthalmic Drugs Advisory committees will meet in joint session to discuss REMS-related topics. In the afternoon of this meeting, the Committee members will discuss what the Agency has learned about the implementation of REMS including the impact of REMS with ETASU on the healthcare system and patient access, and how programs with ETASU can be better integrated into existing health systems.

### **2.2 Issues for Committee Consideration**

The Committee will evaluate the ETASU to assess whether its elements: 1) assure safe use of the drug, 2) are not unduly burdensome on patient access to the drug; and 3) to the extent practicable, minimize the burden on the health care delivery system.

In the afternoon of this meeting, the committee members will be asked to participate in a discussion about the general REMS implementation findings to help improve the implementation of future REMS programs and their assessment metrics.

### **2.3 Risk Evaluation and Mitigation Strategies (REMS)**

The Food and Drug Administration Amendments Act (FDAAA) of 2007 provides FDA the authority to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. The elements of a REMS can include: a Medication Guide, patient package insert (PPI), communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA-approved patient labeling. A Medication Guide can be required as part of approved labeling if FDA determines one or more of the following apply: 1) patient labeling

could help prevent serious adverse events, 2) the product has serious risks that could affect a patient's decision to use or continue to use the drug, or 3) patient adherence to directions is crucial to product effectiveness. A Medication Guide can be required as part of a REMS if FDA determines that it is necessary to ensure the benefits of the drug outweigh the risks.<sup>1</sup>

The REMS can include a communication plan when it is determined that such a plan may support implementation of the REMS or when information about the serious risks should be disseminated to health care providers. The information provided may include letters to health care providers; disseminating information about REMS elements to explain certain safety protocols; or dissemination of information to health care providers through professional societies.

Elements to assure safe use are put in place when the FDA determines that the drug can be approved only if, or would be withdrawn unless, such elements were required. There are six elements that can be included in a REMS with ETASU: 1) health care providers who prescribe the drug have particular training or experience, or are specially certified, 2) pharmacies, practitioners, or health care settings that dispense the drug are specially certified, 3) the drug is to be dispensed to patients only in certain health care settings, such as hospitals, 4) the drug is to be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results, 5) each patient using the drug is to be subject to certain monitoring, or 6) each patient using the drug is to be enrolled in a registry.

All approved REMS include one or more goals and can include one or more elements to mitigate the serious risk. All REMS for NDAs and BLAs must include a timetable for submission of assessment of the REMS. The assessments are required to be submitted to FDA at a minimum by 18 months, by 3 years and within the 7<sup>th</sup> year from approval of the REMS. The assessments can be required more frequently and can be eliminated after 3 years.

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<sup>1</sup> After initially requiring Medication Guides as elements of REMS in all cases in which a Medication Guide was found to be necessary under the criteria in 21 CFR Part 208, the Agency plans to publish a final guidance in November 2011 stating that Medication Guides will normally be part of a REMS only when the REMS includes elements to assure safe use.

From the implementation of the FDAAA REMS provisions on March 25, 2008 until October 7, 2011, approximately 185 products were approved with a REMS. Most include only a Medication Guide and a timetable for submission of assessments; these have been referred to as “Medication Guide-only” REMS.<sup>2</sup> Forty REMS were approved with a communication plan as the primary element and 21 with ETASU. There are an additional ten deemed REMS that have been approved, including the Istotretinoin REMS.<sup>3</sup>

### **3 General Issues Related to the Impact of REMS with Elements to Assure Safe Use (ETASU)**

#### **3.1 Listing of REMS with ETASU**

There are 21 approved REMS that have elements to assure safe use, and ten deemed REMS approved. The table in the Appendix provides a summary of each of these REMS, listing the elements included in each REMS. A publicly available website provides an updated listing of all approved REMS<sup>4</sup> and another publicly available website provides access to the REMS approval letters<sup>5</sup>.

#### **3.2 Aggregated findings from REMS assessments**

Since March 25, 2008 the Agency has reviewed 125 REMS assessment reports; 54 are for Medication Guide-only REMS, 24 are for REMS with a communication plan with or without Medication Guide, and 47 are for REMS with ETASU with or without Medication Guide/communication plan. Because several of these products, predominantly the drugs with ETASU, have timetables for submission of assessments at closely spaced intervals, many of these assessment reports represent multiple assessments of the same product.

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<sup>2</sup> Since February 2011, 75 “Medication Guide-only” REMS have been released.

<sup>3</sup> Section 909(b)(1) of FDAAA specifies that a drug that was approved before the effective date of this Act is deemed to have in effect an approved REMS under section 505–1 of the FDCA if there are in effect on the effective date of this Act elements to assure safe use— (A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or (B) otherwise agreed to by the applicant and the Secretary [of Health and Human Services] for such drug. Sponsors were required to submit a proposed REMS no later than 180 days after the effective date of this Act, for FDA to review and approve.

<sup>4</sup> [www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm)

<sup>5</sup> <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

REMS assessment reports provide information to determine if the goals of the REMS are being met. For example, the assessment plans for REMS with ETASU often include summaries of adverse events of interest; statistics on enrollment of prescribers, pharmacies, health care settings, and/or patients; discontinuation statistics; measures of compliance with procedures; drug use; measures of delays in patient receipt of drug; and summaries of audits and interventions when non-compliance has been identified.

The assessments of REMS with ETASU highlight the challenges of determining the effectiveness of the REMS. In many cases the goals of REMS relate to supporting informed decisions, informing patients and prescribers about important risks, and ensuring that certain processes are conducted (baseline ophthalmologic evaluations, pregnancy testing). Assessments have identified a need to revise forms and some processes. The REMS with goals that relate to reducing risk of certain outcomes (myocardial infarction, fetal harm due to pregnancy exposure, vision loss, hepatotoxicity) are much more difficult to assess. The assessments of outcomes are difficult to measure because often the outcomes are rare, the drug use is limited, the time from approval is too short for an adequate assessment, there is no baseline for comparison, and/or the events may not be reported. In addition, it is difficult to determine whether the REMS itself is having the intended effect or whether other factors are determining the outcomes.

Using the REMS assessments to assess the impact on patient access to the drug and provider burden has provided limited information. In some cases, the assessments have provided information on delays in drug dispensing because of problems with certain REMS processes, but other measures of problems with access and burden have generally not been included in REMS assessment reports.

### **3.3 Summary of stakeholder input related to integration of REMS into healthcare systems**

REMS with ETASUs are complex programs that require implementation by various stakeholders in the healthcare delivery system. Since the approval of the first REMS with ETASU in 2008, several challenges have been identified by stakeholders as these programs were integrated into the healthcare delivery system. Input regarding these challenges has been received by the Agency from professional societies, healthcare professionals, patients, and various managed

care organizations at public and internal FDA meetings as well as professional society meetings.

A summary of the challenges identified by stakeholders regarding integration of REMS with ETASU into the healthcare delivery system is as follows:

- Lack of standardization due to the approval of multiple programs with unique requirements that often require different systems to manage and support
- Disruption in workflow
- Need to enroll in multiple programs that are used to manage the same risk
- Extensive training/education requirements and counseling requirements without compensation
- High administrative costs and burden with no compensation for complying with REMS requirements
- Incompatibility of required forms with existing systems
- Inability of inpatient pharmacies and closed healthcare systems to obtain drug
- Inability to delegate REMS-related tasks to office staff and inability to assign a proxy for covering prescribers
- Inability to order emergency supply of drug for patients urgently admitted to a hospital

Each of these challenges may result in burden on the healthcare system and/or reduced or delayed patient access to medically necessary drugs.

The challenges should be prioritized and the approaches to improve integration of REMS into the healthcare delivery system should be explored with the ultimate goal of minimizing burden to the healthcare system and improving patient access to the drug, while effectively managing the risk of the drug.

### **3.4 Assessing the impact of REMS on burden and access**

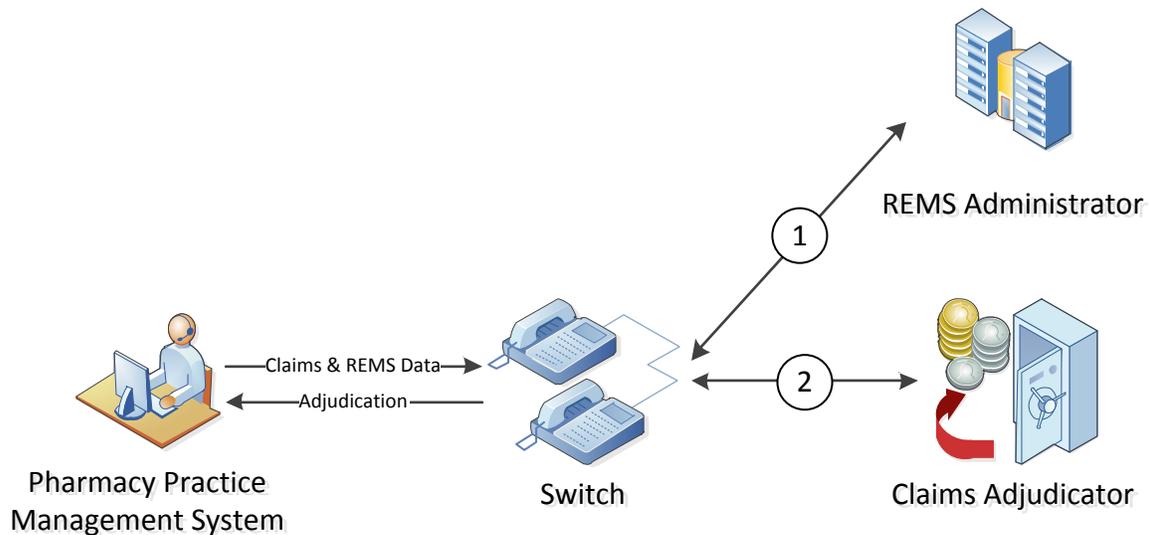
All REMS with ETASU, by their nature, impose at least some level of burden on the healthcare delivery system by requiring that providers, pharmacists and patients take steps to help assure safe use of the medication. The FDA will present its perspectives on the administrative burdens of REMS with ETASU and their impact on access to drugs.

### **3.5 Pharmacy Systems**

In previous public meetings, pharmacy stakeholders have requested that FDA take steps to better integrate REMS into their pharmacy practice management systems. In their day-to-day practice, community and retail pharmacists rely heavily on these computerized systems for a variety of tasks, including entry of patient and prescription data, filing of claims with insurers, identification of potential drug-drug interactions, and receipt of e-prescriptions. The majority of pharmacy management systems communicate with insurers and prescribers using well-defined telecommunications standards established by standards-setting organizations such as the National Council for Prescription Drug Programs (NCPDP).

Pharmacy practice management systems play an important role in electronic prescription drug claims adjudication. Once a pharmacy receives an insured patient's prescription and insurance information, this data is sent to a pharmacy "switch." The switch acts as a virtual "post-office" for claims data, routing the claim to the appropriate insurer. The insurer then inspects the claim and sends payment data back to the pharmacist via the switch. This transaction takes only seconds, allowing pharmacies and patients to know whether or not the patient's insurer will pay for a claim by the time the patient arrives to pick up his or her prescription.

It has been proposed that the pharmacy practice management system, in conjunction with the pharmacy switch, be used to verify safe use conditions in a REMS in a manner similar to the way that a pharmacy systems currently adjudicate claims. A simplified model of this process is shown below.



The process works as follows: when prescription information is entered into the pharmacy system, the pharmacy system automatically determines whether the drug has a REMS. If so, the pharmacy system submits REMS-relevant information to the switch along with any information necessary for claims adjudication. The switch then forwards that information to the "REMS Administrator", the party responsible for managing the operations for the REMS. The REMS Administrator identifies whether safe use conditions for the REMS have been met (e.g., whether a prescriber has been enrolled and whether patient monitoring has taken place). If so, the switch will proceed with the normal claims adjudication process if necessary. If REMS requirements have not been met, the switch returns a message to the pharmacist informing them of which requirement has not been met and steps that the pharmacist, prescriber or patient can take to resolve the issue.

The afternoon session will include a discussion of options for decreasing the burden of REMS with ETASU using pharmacy systems.

#### 4 APPENDIX:

TABLE: Listing of Approved REMS with Elements to Assure Safe Use (ETASU)

- A. Healthcare providers who prescribe the drug have particular training or experience, or are specially certified
- B. Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- C. The drug be dispensed to patients only in certain healthcare settings, such as hospitals
- D. The drug be dispensed only to patients with evidence or other documentation of safe-use conditions, such as laboratory test results
- E. Each patient using the drug be subject to certain monitoring
- F. Each patient using the drug be enrolled in a registry

| Drug  | ETASU |   |   |   |   |   |
|---|-------|---|---|---|---|---|
|   | A     | B | C | D | E | F |
| Abstral (fentanyl)  | ✓     | ✓ |   | ✓ |   |   |
| *Actiq (fentanyl citrate)   | ✓     | ✓ |   | ✓ |   |   |
| Aranesp (darbepoetin alfa)  | ✓     | ✓ |   | ✓ |   |   |
| Avandamet, Avandaryl, Avandia (rosiglitazone-containing products) | ✓     | ✓ |   | ✓ |   |   |
| Butrans (buprenorphine)   | ✓     |   |   |   |   |   |
| Caprelsa (vandetanib)   | ✓     | ✓ |   |   |   |   |
| Entereg (alvimopan)   |       | ✓ | ✓ | ✓ |   |   |
| Epogen/Procrit (epoetin alfa)                                     | ✓     | ✓ |   | ✓ |   |   |
| Exalgo (hydromorphone)  | ✓     |   |   |   |   |   |
| Extraneal (icodextrin)  |       |   |   | ✓ |   |   |
| Fentora (fentanyl citrate)  | ✓     | ✓ |   | ✓ |   |   |
| *Isotretinoin   | ✓     | ✓ |   | ✓ |   | ✓ |
| Lazanda (fentanyl)  | ✓     | ✓ |   | ✓ |   |   |
| *Letairis (ambrisentan)   | ✓     | ✓ |   | ✓ |   |   |
| *Lotronex (alosetron)   | ✓     |   |   | ✓ |   |   |

\* Federal Register published on March 27, 2008 identified this drug deemed to have a REM

| Drug                                 | ETASU |   |   |   |   |   |
|--------------------------------------|-------|---|---|---|---|---|
|                                      | A     | B | C | D | E | F |
| Lumizyme (alglucosidase alfa)        | ✓     | ✓ |   | ✓ |   | ✓ |
| *Mifeprex (mifepristone)             | ✓     |   | ✓ | ✓ |   |   |
| Nplate (romiplostim)                 | ✓     | ✓ |   | ✓ | ✓ |   |
| Nucynta ER (tapentadol)              | ✓     |   |   |   |   |   |
| Onsolis (fentanyl)                   | ✓     | ✓ |   | ✓ |   |   |
| Oxycontin (oxycodone)                | ✓     |   |   |   |   |   |
| Promacta (eltrombopag)               | ✓     | ✓ | ✓ | ✓ | ✓ |   |
| *Revlimid (lenalidomide)             | ✓     | ✓ |   | ✓ |   | ✓ |
| Sabril (vigabatrin)                  | ✓     | ✓ |   | ✓ |   | ✓ |
| Soliris (eculizumab)                 | ✓     |   |   |   |   |   |
| Suboxone<br>(buprenorphine/naloxone) |       |   |   | ✓ | ✓ |   |
| *Thalomid (thalidomide)              | ✓     | ✓ |   | ✓ |   | ✓ |
| *Tikosyn (dofetilide)                | ✓     | ✓ |   |   |   |   |
| *Tracleer (bosentan)                 | ✓     | ✓ |   | ✓ |   |   |
| *Tysabri (natalizumab)               | ✓     | ✓ |   | ✓ |   |   |
| Zyprexa Relprevv (olanzapine)        | ✓     | ✓ | ✓ | ✓ | ✓ | ✓ |

\* Federal Register published on March 27, 2008 identified this drug as deemed to have a REMS.