

## CHAPTER 11

# RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

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The Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER) are the departments within the Food and Drug Administration (FDA) responsible for evaluating drugs (or biologics in the case of CBER) to make sure they are not only effective but safe for human use. Every prescription and over-the-counter medication is evaluated by CDER or CBER prior to market.<sup>1</sup> There are drugs that, although they have substantial therapeutic benefits, carry significant risks. To ensure that the benefits outweigh the risks, the FDA may require manufacturers to go beyond product labeling and implement special restricted access programs.

Risk management programs have been around since the early 1990s. One of the first medications to have prescribing and dispensing restrictions is clozapine (Clozaril®).<sup>2</sup> This antipsychotic significantly increases a patient's risk for agranulocytosis, so patients must obtain weekly blood counts to receive the drug. Physicians must monitor and submit lab results to the manufacturer's restricted access program in order to receive prescribing authority. The amount of clozapine dispensed is limited to the number of days until the next lab draw. Patients, physicians, and pharmacies must be registered with clozapine's "no blood, no drug" program to ensure compliance.<sup>2</sup>

Historically, such risk management programs were called Risk Minimization Action Plans (RiskMAPs). The Prescription Drug User Fee Act (PDUFA III) of 2002 allowed the FDA to suggest RiskMAP programs for drugs that might not otherwise be allowed on the market because of significant safety concerns. RiskMAPs were tools "...designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits."<sup>3</sup> Examples of these tools include targeted education, reminder systems, and performance-linked access systems (eg. clozapine's "no blood, no drug" program). Although effective, there were limitations to the program. RiskMAPs were voluntary and the FDA could only recommend a risk minimization program. They had no authority to require a manufacturer to comply, nor could they require postmarketing studies, labeling changes, or other safety communications. The FDA Amendments Act of 2007 expanded the FDA's authority regarding drug safety. A section of the legislation now allows the FDA to require

postmarketing studies and to mandate Risk Evaluation and Mitigation Strategies (REMS) for drugs that have the potential to cause serious patient harm.<sup>2,4</sup>

## **WHAT ARE REMS?**

REMS are strategies designed to mitigate a known or potentially serious risk associated with a drug or biologic product.<sup>5</sup> When determining whether or not a REMS is needed, the FDA takes into consideration the number of patients who would potentially use the drug, the seriousness of the disease or condition it's intended to treat, the duration of treatment, and of course, the expected benefit compared to the severity of its adverse effects.<sup>4</sup> The FDA can base its decision on results from clinical trials, adverse drug event reports, or post-marketing studies.

REMS can be implemented at any stage of the product lifecycle. It can be included as part of a license application for a new drug or new indication, or the FDA can require the implementation of a REMS for drugs already on the market if new safety information becomes available.<sup>6</sup> This is why post-market surveillance is so important. The number of people who participate in pre-market, Phase 3 clinical trials can be small compared to the larger population who ultimately uses the drug. Therefore, continually assessing the efficacy and safety of drugs post-market is necessary to identify any potential safety concerns not known at the time of a drug's approval process.

The FDA can mandate a REMS for drugs they feel need additional safety measures beyond that of standard professional labeling. These safety measures are unique to each drug or therapeutic class. Therefore, no two REMS are exactly alike. The following are potential elements of a REMS:<sup>6</sup>

- Medication guide
- Communication plan
- Elements to assure safe use (ETASU)
- Implementation system

Once a REMS is approved, it is enforceable. The FDA has the authority to hold the manufacturer accountable for not complying. If the manufacturer fails to implement a REMS, they can be fined. The FDA can also restrict its use by preventing the sale of the drug and/or consider it misbranded.<sup>4</sup>

## **REMS REQUIREMENTS**

A REMS can contain any one element or a combination of elements listed above. The specific

components of a REMS can vary based on several factors, including the severity of the drug's potential adverse effects and the population likely to use it.<sup>6</sup>

## Medication Guides

A medication guide is a handout written in patient-friendly language by the manufacturer highlighting important safety or efficacy information about a drug product. These are not the same as Consumer Medication Information sheet (CMI) which provide general information about all aspects of a prescription drug. Unlike CMIs, which are written by organizations or the private sector without review by the FDA, medication guides are written specifically for a drug product by its drug manufacturer. Since each medication guide is approved by the FDA, they are not interchangeable. Substitution of one manufacturer's medication guide for another is discouraged, even though the content for a generic drug may be similar to that of its brand name equivalent.

Medication guides may be related to safety, addressing potentially serious risks patients should be aware of prior to taking the drug or they can be about efficacy, where patient adherence to directions for use is important to a drug's effectiveness. The FDA determines whether or not a medication guide is required. Although close to 300 drug products have medication guides, only a small portion are part of a REMS. Typically, medication guides that are part of a REMS include an Element to Assure Safe Use (ETASU), which often have more stringent requirements.

If required, medication guides must be dispensed with every new prescription and with each refill. They do not, however, have to be given to patients in an inpatient setting (eg. hospital, nursing home) since the medication is being administered by a healthcare professional. The only exception is if the patient requests one or if the medication guide is part of a REMS that requires distribution to inpatients. In other settings where medications are dispensed to a healthcare professional for administration to a patient, medication guides are only required when the patient is receiving the medication for the first time or if the medication guide has been updated with new information. Examples of such settings include dialysis centers, physician offices, chemotherapy infusion clinics, home health care, etc.<sup>7</sup>

Setting	Patient or Patient's Agent Requests Medication Guide	Medication Guide Provided Each Time Drug Dispensed	Medication Guide Provided at Time of First Dispensing	Medication Guide Provided when Medication Guide Materially Changed	Drug is Subject to an ETASU REMS that includes Specific Requirements for Providing and Reviewing a Medication Guide
<b>Inpatient</b>	Must provide medication guide	FDA intends to exercise enforcement discretion; Medication guide need not be provided	FDA intends to exercise enforcement discretion; Medication guide need not be provided	FDA intends to exercise enforcement discretion; Medication guide need not be provided	Must provide medication guide as specified in REMS
<b>Outpatient when drug dispensed to healthcare professional for administration to patient</b> (e.g., clinic, infusion center, emergency department, outpatient surgery)	Must provide medication guide	FDA intends to exercise enforcement discretion; Medication guide need not be provided	Must provide medication guide	Must provide medication guide	Must provide medication guide as specified in REMS
<b>Outpatient when drug dispensed directly to caregiver</b> (e.g., retail pharmacy, hospital ambulatory pharmacy, patient samples)	Must provide medication guide	Must provide medication guide	Must provide medication guide	Must provide medication guide	Must provide medication guide as specified in REMS

**Table 11-1.** Medication guide enforcement discretion policy<sup>7</sup>

## Communication Plan

While a medication guide educates patients, a communication plan is a REMS element that informs healthcare professionals about the safe and effective use of a drug product. Manufacturers use communication plans to inform health care providers about the risks of a drug. They are also used to educate them about REMS elements, such as the use of periodic laboratory tests for medical monitoring, and encourage implementation. Communication plans typically involve sending “Dear Healthcare Professional” letters. These are sent directly to the health care provider, disseminated through professional organizations, or distributed to specific practice settings. Communication Plans may also include training materials or presentations. Health care providers are then supposed to use the information to promote appropriate use of the drug and reinforce patient compliance.

The antidiabetic agent liraglutide (Saxenda®) is an example of a medication with a Communication Plan.<sup>5</sup> This REMS is required so that healthcare professionals are aware of liraglutide’s increased risk of thyroid carcinoma and acute pancreatitis.<sup>8</sup> The manufacturer’s Communication Plan for this drug includes a Dear Healthcare Professional letter, web-based information, and dissemination of a letter to professional organizations.

## Elements to Assure Safe Use

The most complicated and extensive component of a REMS is the Element to Assure Safe Use (ETASU). As defined by the FDA, they are “strictly controlled systems or requirements put into place to enforce the appropriate use of a drug.”<sup>6</sup> Drugs with ETASUs can be considered potentially harmful if not used appropriately. Therefore, this REMS element allows patients to have access to drugs known to have serious risk that would otherwise not be available.

Every ETASU is different. Medications with an ETASU may require that prescribers have specific training, experience, or be certified before being able to prescribe that drug.<sup>9</sup> Other ETASUs may require special laboratory monitoring and/or enrollment of patients in a drug registry. Still other ETASU may only allow the medication to be dispensed by a specialty pharmacy or dispensed to patients in certain healthcare settings, such as a hospital.

One example of a medication with an ETASU is Aved® (testosterone undecanoate).<sup>5</sup> This injectable product is used to treat adult males with low testosterone levels. The REMS requires that it be administered by a trained healthcare professional in a doctor’s office, clinic, or hospital with on-site access to equipment because of its significant safety risks. Aved® has the potential to cause anaphylaxis as well as pulmonary oil microembolism (POME), which is a serious lung condition that occurs when tiny droplets of castor oil contained in Aved®

travel to the lungs.<sup>10</sup> Since anyone can experience these adverse reactions with any treatment, the ETASU requires that patients stay in the healthcare setting at least 30 minutes after receiving the injection for observation. Additionally, the REMS requires that both the prescriber and healthcare setting complete the REMS certification with an assessment of knowledge before being able to prescribe or administer the drug. The education program includes training on the proper administration of Aved®<sup>®</sup>, information on patient counseling, and understanding of how to manage POME and anaphylaxis.<sup>11</sup> Patients must also be aware of the potential side effects and agree to receive the drug, despite its significant risks.

### Implementation System

All ETASU include an Implementation Plan. This REMS element tells the FDA how the manufacturer plans to monitor patients, practitioners, and healthcare settings to ensure they are being compliant with the ETASU. It is also a way for the manufacturer to evaluate their REMS program and make improvements, if necessary.

For example, the Implementation System for Aved®<sup>®</sup> spells out exactly how the manufacturer will “...maintain, monitor, and evaluate” the REMS to ensure it’s meeting the program’s goals. It includes items such as maintaining a database of all certified healthcare providers, maintaining an informational call center and website, as well as completing an audit of certified healthcare settings. It also includes a timetable for when the manufacturer will submit assessments of the REMS to the FDA.<sup>12</sup>

### Timetable for Submission of Assessments

Assessments are also technically considered a REMS element. They are used to evaluate the effectiveness of a particular REMS. For example, healthcare professionals can be surveyed regarding their understanding of the safe use of a drug. Prescriber compliance with REMS certifications is another assessment tool. Data can also be collected on patient use of a particular drug. Depending on the results, REMS can be modified if the assessment shows changes are needed. REMS can even be eliminated if it has been shown that the REMS was successful at meeting its goals.<sup>6</sup>

### **SHARED SYSTEM REMS**

As of July 2017, there are 70 approved REMS.<sup>5</sup> With so many REMS and each one unique to a particular drug’s manufacturer, it has been very cumbersome for healthcare professionals to comply, especially for drugs with an ETASU. It is time consuming for a physician to make sure he/she has completed the required training before writing a prescription or for a pharmacist

to verify a patient's labs in a registry before dispensing a medication, for example. To minimize the workload and burden on healthcare systems, the FDA has been moving towards the development of standardized REMS. For some identical or closely related drugs (ie. drugs within the same therapeutic class), the FDA has mandated drug companies to develop a single, shared system REMS. Once such example is isotretinoin's iPLEDGE program.<sup>13</sup>

Isotretinoin is a drug used for the treatment of severe acne. Studies have shown a 15-20 week course of therapy to be effective at improving nodular acne. However, isotretinoin is teratogenic and serious birth defects, spontaneous abortion, and premature births have been reported.<sup>14</sup> Therefore, the REMS for isotretinoin informs prescribers, pharmacists, and patients about the drug's serious safety risks and safe-use conditions with the goal of preventing fetal exposure to isotretinoin. In the past, every manufacturer of isotretinoin, brand and generic, had their own REMS each with different ETASU. This made prescribing and dispensing isotretinoin extremely challenging and frustrating. To consolidate and simplify the process, the FDA requested that all the manufacturers of isotretinoin products work together to create one standardized REMS. This single, shared system REMS, called iPLEDGE, includes a medication guide, ETASU, and implementation plan.<sup>14</sup>

Prescribers, pharmacies, patients, and wholesalers must all be registered with the iPLEDGE program.<sup>14</sup> It is a computer-based program that tracks and verifies the critical elements of the program. Prior to receiving the medication, females must commit to 2 simultaneous forms of birth control. They must also complete Patient Monthly Comprehension Questions and a pregnancy test before each prescription.<sup>15</sup> Physicians then enter the results of the pregnancy test and the patient's forms of contraception into iPLEDGE. The pharmacist must obtain verification from iPLEDGE before given authorization to dispense isotretinoin to the patient. Since patients are required to meet these same criteria every month, refills are not allowed and only a 30 day supply can be dispensed.<sup>15</sup>

## **REMS FOR OPIOID PRODUCTS**

There are several other single, shared system REMS including a number of class-wide programs for opioid agents. Not only were these designed to streamline the REMS process, but the opioid REMS are part of a larger, federal initiative aimed at reducing prescription drug abuse, misuse, and overdose. Extended-release and long-acting (ER/LA) opioid products were identified as a subset of opioids at high risk of abuse and misuse, while simultaneously having a high volume of use. The misuse and abuse of this potent class of drugs led to a significant health crisis of addiction, overdose, and death. According to the CDC, 40 people die every day from prescription painkiller abuse. As a result, a class-wide REMS was

introduced for all ER/LA opioid products and their generic equivalents.<sup>16</sup>

The purpose of the ER/LA Opioid Analgesics REMS is to reduce risks while maintaining patient access.<sup>17</sup> This potent class of drugs is intended to manage chronic pain and serious medical conditions, so it's important that these products continue to be available for patients with these conditions. Unfortunately, they often lead to improper use and then abuse. One in 20 individuals age 12 and older admit to taking prescription opioids for non-medical use.<sup>18</sup> It is thought that prescribers are contributing to this abuse and misuse epidemic, as the number of painkillers prescribed over the past 15 years has quadrupled.<sup>19</sup> As a result, prescriber education and patient awareness are the main components of the ER/LA Opioid REMS.

Currently, prescribers are not required to complete the training associated with ER/LA Opioid REMS; however, it is "strongly encouraged".<sup>20</sup> In addition to educating prescribers on proper pain management and patient selection, the REMS education program includes patient counseling tips. Patients should be aware of opioids' addiction potential, informed on the proper disposal of expired or unused medications, and the need to lock them away when not being used.<sup>21</sup>



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