Risk Evaluation and Mitigation Strategies (REMS)

Elaine Lippmann, J.D.
Office of Regulatory Policy, CDER, FDA

Disclaimer: The views and opinions expressed in this presentation are those of the individual presenter and should not be construed to represent FDA’s views or policies.
Agenda

1. Overview of REMS
   a) Purpose
   b) Legal authority
   c) Tools they employ

2. REMS Assessments and Modifications

3. REMS Requirements for Generics
   a) The single, shared system requirement
   b) Waivers of the single, shared system requirement
What is a REMS?

- **Risk Evaluation and Mitigation Strategy**

- Authority given by the FDA Amendments Act (FDAAA) in 2007 (Section 505-1 of the FD&C Act)

- A required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks.
### Examples of the Types of Risk
REMS Requirements Aim to Mitigate

<table>
<thead>
<tr>
<th>Risk Example</th>
<th>Possible REMS Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infection</td>
<td>Patient education on initial warning signs prior to prescribing</td>
</tr>
<tr>
<td>Severe allergic reaction</td>
<td>Healthcare professional must be certified prior to administering the product</td>
</tr>
<tr>
<td>Liver damage</td>
<td>Liver function monitoring while patient is taking the drug</td>
</tr>
<tr>
<td>Severe birth defects</td>
<td>Negative pregnancy test prior to dispensing each prescription</td>
</tr>
</tbody>
</table>
When FDA Can Require a REMS

• Before approval if FDA determines a REMS is necessary to ensure the benefits of the drug outweigh the risks

• Post-approval if FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks
REMS: Key Points

• Drug sponsors develop REMS programs, FDA reviews and approves them
• REMS programs can be designed for a single drug or a class of drugs
• Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs
Possible Components of a REMS

A REMS can include one or more of the following:

• Medication Guide (MG) or Patient Package Insert

• Communication Plan (CP) for Healthcare Providers

• Elements to Assure Safe Use (ETASU)

• Implementation System
Medication Guide

• Provides FDA-approved *patient-friendly* labeling
• Must meet requirements of 21 CFR 208: MG can be required if FDA determines one or more:
  – Patient labeling could help prevent serious adverse events
  – The product has serious risks that could affect patient’s decision to use or continue to use
  – Patient adherence to directions is crucial to product effectiveness
Medication Guide

**TRADENAME** [Insert phonetic spelling] (chemical name) [Insert dosage form], CII

**TRADENAME is:**
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

**Important information about TRADENAME:**
- Get emergency help right away if you take too much TRADENAME (overdose). When you first start taking TRADENAME, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

**Do not take TRADENAME if you have:**
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

**Before taking TRADENAME, tell your healthcare provider if you have a history of:**
- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
- pregnant or planning to become pregnant. Prolonged use of TRADENAME during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- breastfeeding. TRADENAME passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking TRADENAME with certain other medicines can cause serious side effects that could lead to death.

**When taking TRADENAME:**
- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take your prescribed dose [insert frequency, e.g., every X hours at the same time every day]. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Swallow TRADENAME whole. Do not cut, break, chew, crush, dissolve, snort, or inject TRADENAME because this may cause you to overdose and die.
- Call your healthcare provider if the dose you are taking does not control your pain.
- Do not stop taking TRADENAME without talking to your healthcare provider.
- After you stop taking TRADENAME, flush any unused [insert dosage form] down the toilet.

**While taking TRADENAME DO NOT:**
- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with TRADENAME may cause you to overdose and die.

**The possible side effects of TRADENAME:**
- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.
- Get emergency medical help if you have:
  - trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1086. For more information go to dailymed.nlm.nih.gov

Manufactured by [insert name and address] and distributed by [insert name and address]. www.TRADENAME.com or call 1-500-XXX-XXXX

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Examples of REMS with Med Guide

• Xarelto (rivaroxaban)
  – MG, CP, timetable
    • Goal: To inform nonvalvular atrial fibrillation patients that XARELTO should not be stopped without first informing their healthcare professional so as to minimize the risks of post-discontinuation thrombotic events.

• AndroGel (testosterone gel)
  – MG and timetable
    • Goal: To inform patients about the serious risks associated with the use of AndroGel
Communication Plan

• FDA-approved materials used to aid sponsor’s implementation of REMS and/or inform healthcare providers about risks
  – Cannot be directed to patients

• Communication plan may include:
  – “Dear Healthcare Professional” letters
  – Dissemination of information to HCPs through professional societies
  – Information about the REMS to encourage implementation
Example of Communication Plan

• Arcapta Neohaler (indacaterol maleate)
  • Goals:
    – To inform healthcare providers and prescribers of the increased risk of asthma related death and serious outcomes with the long-acting beta2-adrenergic agonists (LABAs) including ARCAPTA NEOHALER when used to treat asthma.
    – To inform healthcare providers and prescribers of the appropriate use of ARCAPTA NEOHALER, and its approved indication (COPD).
Elements to Assure Safe Use (ETASU)

ETASU are required medical interventions or other actions by healthcare professionals prior to prescribing or dispensing the drug. Some actions may also be required in order for the patient to continue on treatment.
Elements to Assure Safe Use (ETASU)

Depending on the risk, a REMS may require any or all of the following:

A. Certification or specialized training of HCPs who prescribe the drug
B. Certification of pharmacies or other dispensers of the drug
C. Dispensing/administration of drug in limited settings e.g., hospitals
D. Dispensing/administration of drug only with evidence of safe-use conditions
E. Each patient using the drug is subject to certain monitoring
F. Enrollment of treated patients in registries
Example of REMS with ETASU

- Sabril (vigabatrin)
  - For the treatment of epilepsy and infantile spasms
  - Risk of new and worsening vision loss, including permanent vision loss
  - ETASU:
    - Prescriber certification
    - Pharmacy certification
    - Patient enrollment
    - Periodic vision assessment
    - Assessment of patient’s response to Sabril
Example of REMS with ETASU

• Letairis (ambrisentan)
  – For the treatment of pulmonary arterial hypertension (PAH)
  – Risk of birth defects
  – ETASU:
    • Provider certification
    • Pharmacy certification
    • Patient enrollment and monitoring
Implementation Systems

• REMS may include an implementation system related to the following ETASU:
  – Certification of pharmacies and hospitals
  – Healthcare settings
  – Safe use conditions

• May require applicant to take reasonable steps to—
  – Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and
  – Work to improve implementation of such elements by such persons
Timetable for Submission of Assessments

• Every REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS (505-1(d))
• The timetable for submission of assessments must include an assessment
  – by 18 months, 3 years, and in the 7th year after the REMS is initially approved
• REMS can require additional assessments
• Can be eliminated after three years
REMS Assessments

Must include:

With respect to each REMS goal, an assessment of the extent to which the REMS is meeting the goal or whether one or more goals/elements should be modified.
Information Provided in Assessments: Examples

• Survey data
• Summary of adverse events
• Prescriber compliance
• Use data
• Number and percentages of patients who were monitored for potential serious adverse events during treatment with the drug
REMS Modification

• Applicant may submit REMS modification proposing addition, modification, or removal of any goal or element
  – Must include adequate rationale for proposal

• FDA must review/act on REMS mods within timeframes specified in Guidance
  (Risk Evaluation and Mitigation Strategies: Modifications and Revisions, April 2015)
REMS Modification

• After REMS is approved, FDA may require submission of a proposed modification if FDA determines that 1 or more goals or elements should be added, modified, or removed from the REMS to:
  – Ensure the benefits of the drug outweigh the risks
  – Minimize the burden on the health care delivery system of complying with the REMS
REMS requirements for generics (ANDA)

- Where innovator product is subject to REMS, ANDA referencing that product is subject to:
  - Med Guide
  - ETASU

- ANDA must use a *single, shared system* with the innovator for any ETASU (unless FDA waives this requirement, in which case ANDA can use different, but comparable system)
Single Shared System REMS

• NDA and all ANDAs
• Single REMS document, REMS materials (except MGs), and supporting documents applicable to all drugs
• Shared database and infrastructure
Benefits of a single shared system

• Reduces burden for different stakeholders
  – single portal to access materials and other documentation and information about the program
  – prescribers, pharmacies, and healthcare settings complete certification and other administrative requirements once rather than for each individual drug

• Potential for cost sharing among all sponsors
SSS Development Process

1. FDA notifies applicant of REMS requirement
2. ANDA applicant contact RLD holder
3. Kick-off meeting
4. Companies form industry working group
5. Agency forms review team
6. FDA facilitates when needed
7. REMS submission
SSS Development Process

1. The Office of Generic Drugs (OGD) notifies each ANDA sponsor of the requirement for a SSS by sending a REMS notification letter.

   - The REMS notification letter (1) notifies the ANDA sponsor of the requirement of a SSS, and (2) directs the ANDA sponsor to contact the sponsor of the reference listed drug.
SSS REMS Development Process (Cont’d)

2. ANDA holders make initial contact with RLD holder and initiate discussions about a SSS REMS

3. FDA hosts a “kick-off” meeting to convey expectations and facilitate planning to move SSS REMS development forward
SSS REMS Development Process (Cont’d)

4. Companies may form an “industry working group” (IWG) to develop a proposal for the shared REMS
   – FDA instructs the IWG sponsors to identify a single point of contact to represent the IWG, and emphasizes the importance of first working out the cost and governance structures
   – IWG provides bi-weekly updates to the Agency

5. The Agency forms a REMS review team including staff from a number of Offices within the Center
   – FDA communicates expected timeframes for milestones
   – FDA schedules periodic teleconferences with the IWG
SSS REMS Development Process (Cont’d)

6. When a company indicates to the Agency that another company (brand or generic) in the IWG is not receptive or responsive to efforts to develop a SSS REMS, the Agency may serve as facilitator to aid in reaching resolution.

7. Once developed, the SSS REMS proposal is submitted by the innovator and generic companies to the Agency for review.
   – FDA instructs the IWG how to submit the REMS proposal.
Issues to be Addressed in Negotiations

• Cost-sharing
• Confidentiality
• Product liability concerns
• Anti-trust concerns
• Access to a license for elements protected by patent
• Experience/trust gap(s)
FDA Perspective on Waiver

• Shared system REMS fulfill Congressional intent to reduce end-user burden and foster ease of access to generic products with REMS.

• The waiver provision provides an alternative path for approval of generic drugs if a single shared system is not feasible.
Waiver of the SSS Requirement

• Expectation is successful formation of SSS
• If, during the course of negotiations, FDA or the sponsors believe that a waiver may be warranted, FDA will:
  – Determine whether the statutory criteria for a waiver have been met
  – Review a separate proposed REMS submission by the ANDA sponsor(s)
Criteria for Waiver

The Secretary **may waive the requirement** for a drug that is the subject of an abbreviated new drug application, and permit the applicant to **use a different, comparable aspect** of the elements to assure safe use, if the Secretary determines that—

— (i) the **burden of creating a single, shared system outweighs the benefit.** . . . taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product; or
Criteria for Waiver

...(ii) an aspect of the elements to assure safe use for the applicable listed drug is **claimed by a patent** that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the applicant for the abbreviated new drug application certifies that it has **sought a license for use** of an aspect of the elements to assure safe use for the applicable listed drug and that it was **unable to obtain a license**.
Separate REMS for ANDA(s)

FDA may waive the requirement for a SSS and permit the ANDA to use a “different, comparable aspect” of the ETASU (505-1(i)).
Separate REMS for ANDA(s)

• Same goals

• Same ETASU
  – Must achieve same level of safety
  – How the elements are operationalized may differ
  – Applicants should explain and justify any differences in operations
Separate REMS for ANDA(s)

Things to consider in developing a separate REMS program:

• Will the operational differences shift burden to other stakeholders?

• Will the operational differences cause confusion for stakeholders?

• Will the operations allow for other ANDAs to join the program?
Waiver Process

- FDA may waive the SSS requirement upon request from a sponsor.
- FDA may determine on its own that waiver is appropriate without receiving a request from a sponsor.
- In each circumstance, FDA conducts an individual analysis based on the statutory criteria for waiving the SSS requirement.
A Complete REMS Submission

• REMS
• REMS Supporting Document
• Appended materials
Proposed REMS

The REMS includes the necessary elements that support the safe use of the product.

- Goals
- Elements to assure safe use
- Implementation system
- Any materials that are referenced in the REMS
  - Training programs
  - Enrollment forms
  - Patient agreement forms
  - Medication Guide
REMS Supporting Document

Describes how the program is being implemented

• Whether the element or tools used are compatible with the established distribution, procurement and dispensing systems

• A description of the effectiveness of the proposed program

• Includes metrics that will be used to determine or identify problems with the program and if the goals are being met

• Criteria, methodology or polices that address your management or implementation
Conclusion

• REMS are a valuable tool for patient safety
• They can employ a variety of tools to ensure benefits of a drug outweigh risks
• They are specifically tailored to a particular drug and particular risk
• REMS programs are often shared by multiple sponsors (e.g., ANDAs and innovators)
Information For Industry

Click for:

• REMS Provision in FD&C Act
• FDA REMS Website
• FDA Guidance Documents
• FDA Webinar: REMS Basics
• PDF of the slides for today’s sessions
• If we did not get to you question, you can always email to us at:

  CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

Click Here for Evaluation and Certificate

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REMS in Structured Product Labeling Format: An Introduction

Adam Kroetsch

FDA | CDER
January 26, 2017
What is SPL?

SPL is a data standard for capturing information about drug products:

• SPL stands for “Structured Product Labeling” but covers product information beyond labeling
• SPL is developed and maintained by a Standards Development Organization called Health Level Seven International (HL7)

Proposal to capture REMS in SPL format was identified by stakeholders (in particular, the National Council for Prescription Drug Programs) and was adopted in 2014 as a “priority project” towards REMS Standardization.
What is SPL not?

REMS SPL is not currently used for the exchange of patient or healthcare provider-specific information

• For example, prescribers cannot use SPL to enroll in a REMS, prescribe drugs, or monitor patients.

• A related effort, the REMS Platform Standards Initiative, is designed to develop standards to exchange this type of information.
REMS SPL starts with the official “REMS Document”

REMS Document

Initial REMS Approval: 10/08/2013
Most Recent Modification: 6/11/2014

NDA 204819

Adempas® (riociguat tablets)

Bayer Healthcare Pharmaceuticals
P.O. Box 915
Whippany, NJ 07981-0915

Risk Evaluation and Mitigation Strategy (REMS)

I. GOALS

The goals of the Adempas Risk Evaluation and Mitigation Strategy (REMS) are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Adempas
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Adempas
   a. Females who are pregnant must not be prescribed Adempas
   b. Females taking Adempas must not become pregnant

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Adempas prescription in accordance with 21 CFR 208.24.

The Adempas Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare providers (HCPs) who prescribe Adempas will be specially certified.
   a. Bayer will ensure that HCPs who prescribe Adempas are specially certified. HCPs will agree on the Adempas REMS Prescriber Enrollment and Agreement Form to:

Appended Material

Appended Material

Adempas REMS (Risk Evaluation and Mitigation Strategy)

Prescriber Enrollment and Agreement Form

In order to prescribe Adempas, prescribers must enroll in the Adempas REMS Program by completing this form.

Adempas REMS Program information is available at www.adempasREMS.com or by calling 1-855-432-9672.

Prescriber Information:

First Name
Middle Name
Last Name

Address

City, State, ZIP

Phone Number

Email Address

Signature

Date

Adempas REMS (Risk Evaluation and Mitigation Strategy)

4
What REMS SPL Looks Like

1. Healthcare Providers who prescribe [drug/class name] must:

<table>
<thead>
<tr>
<th>To become certified to prescribe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Be able to [clinical activity to be performed].</td>
</tr>
<tr>
<td>2. Review the drug’s Prescribing Information.</td>
</tr>
<tr>
<td>3. Review the following: [List of Prescriber Educational Material(s)].</td>
</tr>
<tr>
<td>4. Receive training provided by [entity providing the training, e.g., the applicant, a CE provider].</td>
</tr>
<tr>
<td>5. Successfully complete the [Knowledge Assessment Form] and submit it to the REMS Program.</td>
</tr>
<tr>
<td>6. Enroll in the REMS by completing the [Enrollment Form] and submitting it to the REMS Program.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before treatment initiation (first dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Counsel the patient on [topic] OR Counsel the patient using [REMS material].</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>8. Provide the patient with the [REMS Material]</td>
</tr>
<tr>
<td>9. Assess the patient’s [condition(s) or health status(es)] OR Assess the patient’s [condition(s) or health status(es)]</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>10. Complete the [Patient Form]. Provide a completed copy of the form to the patient. OR Complete the [Patient Form]. Retain a completed copy in the patient’s record.</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>11. Enroll the patient by completing and submitting the [Patient Enrollment Form] to the REMS program. OR</td>
</tr>
</tbody>
</table>
What REMS SPL Really Looks Like

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            <content ID="R001">1. Be able to [clinical activity to be performed].</content>
            <br/>
            <content ID="R002">2. Review the drug’s Prescribing Information.</content>
            <br/>
            <content ID="R003">3. Review the following: [List of Prescriber Educational Material(s)]</content>
            <br/>
            <content ID="R004">4. Receive training provided by [entity providing the training, e.g.]</content>
            <br/>
            <content ID="R005">5. Successfully complete the [Knowledge Assessment Form] and submit</content>
            <br/>
            <content ID="R006">6. Enroll in the REMS by completing the [Enrollment Form] and submit</content>
          </tr>
        </tbody>
      </table>
      <tr styleCode="Botrule">Before treatment initiation (first dose)</tr>
    </text>
  </section>
</component>
```
Why SPL?

1. Makes REMS information easier to understand.

2. Makes REMS information more accessible.

3. Helps integrate REMS into the care process.
REMS with Elements to Assure Safe Use (ETASU) tend to work similarly

**Prescribers** must:
- Complete training.
- Complete an enrollment form, thereby becoming “certified” to prescribe.
- Counsel and educate patients.
- Make sure patients agree to participate in the REMS and enroll them if necessary.
- Assess or monitor patients to make sure “safe use conditions” are present

**Dispensers** must:
- Complete training.
- Complete an enrollment form, thereby becoming “certified” to dispense.
- Before dispensing, check that “safe use conditions” have been met: e.g., that the prescriber is certified, the patient is enrolled and that any necessary monitoring has been completed.

**Distributors** must:
- Check to make sure dispensers are “certified to dispense” before shipping the drug.
There is little standardization of how REMS are described

- REMS are described in a variety of ways, and REMS requirements are often unclear to stakeholders:
  - The format of REMS documents/materials varies
  - REMS lack consistent terminology
    - Similar concepts often have different names
    - Different concepts may have the same name
    - REMS are often described using regulatory terms like “ETASU”, “Communication Plan” and “Element A-F”, which do not provide useful information about how REMS programs work

- Healthcare providers told us that it was not always easy to find out what was expected of them
REMS SPL captures the “4 W’s” of REMS

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stakeholder (“Who”)</td>
<td>The party that must meet the REMS requirement</td>
<td>prescriber, dispenser, health care setting</td>
</tr>
<tr>
<td>Protocol (“When”)</td>
<td>A particular “stage” in the treatment process around which REMS activities may occur</td>
<td>certification, prescribing, dispensing, administration</td>
</tr>
<tr>
<td>Requirement (“What”)</td>
<td>A clinical or administrative activity that must be performed as part of the REMS</td>
<td>counseling a patient, completing an enrollment form, lab testing</td>
</tr>
<tr>
<td>Material reference (“With What”)</td>
<td>Reference to approved REMS material with which the requirement is carried out</td>
<td>enrollment form, medication guide, educational pamphlet</td>
</tr>
</tbody>
</table>
Using these “4 W’s”, REMS documents are transformed into REMS Summaries

REMS Document Text

To become certified, each prescriber must activate registration, by completing the Prescriber Enrollment Form, via the iPLEDGE website or the automated phone system.

The healthcare provider completes the Healthcare Provider Enrollment Form.

To become certified, each prescriber must complete the Prescriber Enrollment Form

REMS Summaries

1. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
2. Have the authorized representative review the educational materials for dispensers, including Program Overview.
3. Train all relevant staff involved in the dispensing of Drug X using the Program Overview.
4. Establish procedures and procedures to verify dispensing to certified infusion centers only.
5. Enroll in the REMS by completing and submitting the Pharmacy Enrollment Form.

3. Pharmacies that dispense Drug X:

To be able to dispense Drug X:

To be able to dispense Drug X:

Before Drug X:

Before Drug X:

Ongoing:

Ongoing:

Before dispensing:

Before dispensing:

6. Obtain Prescription Ordering Forms from the Drug X REMS Program.
7. Obtain authorization to dispense by calling the Drug X REMS Program.
8. Re-enroll in the Drug X REMS program every 2 years.
9. Do not distribute, transfer, loan, or sell product except to certified dispensers.
10. Cooperate with audits carried out by the sponsor to ensure that all processors and procedures are in place and are being followed.
REMS Summary

The REMS Summary presents the “4 W’s” of the REMS in tabular format:

<table>
<thead>
<tr>
<th>1. Healthcare Providers who prescribe drug X must:</th>
</tr>
</thead>
<tbody>
<tr>
<td>To become certified to prescribe</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Before treatment initiation (first dose)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

REMS Summaries have multiple tables: one for each participant in the REMS.
Why SPL?

1. Makes REMS information easier to understand.

2. Makes REMS information more accessible.

3. Helps integrate REMS into the care process.
REMS SPL information is shared across the healthcare system

SPL data is transmitted from the sponsor to patients, healthcare providers, and the public
REMS SPL unites labeling and REMS information
FDA will be using REMS SPL for its own REMS website

<table>
<thead>
<tr>
<th>Name</th>
<th>Last Updated</th>
<th>Medication Guide*</th>
<th>Communication Plan</th>
<th>ETASU</th>
<th>Implementation System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adasuve <em>(loxapine)</em>, aerosol, powder NDA #022549</td>
<td>10/19/2016</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Addyi <em>( filibanserin)</em>, tablet NDA #022526</td>
<td>05/10/2016</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adempas <em>( riociguat)</em>, tablet, film coated NDA #204819</td>
<td>01/17/2017</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Afrezza <em>(insulin human)</em>, powder, metered NDA #022472</td>
<td>04/01/2016</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alosetron, Shared System REMS</td>
<td>11/22/2016</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Drug Name, NDA number, dosage form**
- **Approval Date**
- **REMS Elements**
Why SPL?

1. Makes REMS information easier to understand.
2. Makes REMS information more accessible.
3. Helps integrate REMS into the care process.
REMS Summaries are transformed into standardized data elements

**REMS Summaries**

**Stakeholder**
- Prescribers

**Protocol**
- To be able to prescribe

**Requirement**
- Enroll in REMS
REMS Summary

1. Healthcare Providers who prescribe drug X must:

To become certified to prescribe:
1. Review the drug’s Prescribing Information.
2. Enroll in the REMS by completing the Drug X REMS Enrollment Form and submitting it to the REMS Program.

Before treatment initiation (first dose):
3. Counsel the patient using Drug X REMS Counseling Material.
4. Assess the patient’s [condition(s) or health status(es)].
REMS Data Elements

The <stakeholder> Data Element uses a standard terminology to describe the role of the participant in the REMS:

- Prescriber
- Dispenser
- Patient
- Distributor
- Other Healthcare Providers (e.g., nurses who treat patients on the drug)
REMS Data Elements

The <protocol> Data Element uses a standard terminology to describe the steps in the REMS and medication use process, such as:

- REMS Certification
- Treatment Initiation
- Dispensing
- Discontinuation

These terms are combined with “modifiers” to specify when a requirement needs to happen: e.g., “before REMS Certification”, “after Treatment Initiation”, “one week after Dispensing”, etc.
REMS Data Elements

The <requirement> Data Element uses a standard terminology to describe the clinical or administrative activities that stakeholders need to carry out in the REMS, such as:

- Enroll in the REMS
- Counsel patient
- Review Prescribing Information
- Get lab test or monitoring
REMS Data Elements

The `<documentReference>` Data Element identifies the material used to carry out the REMS activity. In general, there are three types of “materials” that may be referenced in an SPL document:

- An appended material (e.g., a form or educational material) – typically attached as a PDF
- A website, referenced as a URL
- An electronic data standard
  - Currently NCPDP’s Telecommunications Standard is the only standard available, but more will be added in the future as needed.
Example of codified REMS within SPL

When:
- While prescribing

What:
- Counsel patient

Who:
- Prescriber

With What:
- documentReference
Codified REMS SPL information can be displayed in many different ways

<table>
<thead>
<tr>
<th>Before/During/After</th>
<th>Activity</th>
<th>Stakeholder</th>
<th>Requirement</th>
<th>Document</th>
</tr>
</thead>
<tbody>
<tr>
<td>before</td>
<td>all activity</td>
<td>dispenser</td>
<td>designate authorized representative</td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>all activity</td>
<td>dispenser</td>
<td>Have representative review educational materials</td>
<td>Program Overview</td>
</tr>
<tr>
<td>before</td>
<td>all activity</td>
<td>dispenser</td>
<td>train staff</td>
<td>Program Overview</td>
</tr>
<tr>
<td>before</td>
<td>all activity</td>
<td>dispenser</td>
<td>Establish processes and procedures to verify safe use conditions</td>
<td>Program Overview</td>
</tr>
<tr>
<td>before</td>
<td>all activity</td>
<td>dispenser</td>
<td>Enroll in REMS</td>
<td>Pharmacy Enrollment Form</td>
</tr>
<tr>
<td>before</td>
<td>dispensing</td>
<td>dispenser</td>
<td>obtain dispensing authorization</td>
<td></td>
</tr>
<tr>
<td>every 2 years during</td>
<td>dispensing</td>
<td>dispenser</td>
<td>Enroll in REMS</td>
<td></td>
</tr>
<tr>
<td>during</td>
<td>dispensing</td>
<td>dispenser</td>
<td>ensure dispensing only to certified provider</td>
<td></td>
</tr>
<tr>
<td>during</td>
<td>dispensing</td>
<td>dispenser</td>
<td>Cooperate with audits</td>
<td></td>
</tr>
</tbody>
</table>
Use of REMS SPL in the Healthcare System

Structured REMS data in a format like SPL can help integrate REMS into the healthcare system and ensure stakeholder awareness of and compliance with REMS.

Source: Journal of Managed Care Pharmacy.  
http://www.amcp.org/JMCP/2013/May/16524/1033.html
Use of SPL in the Healthcare System: Prescriber Example

Scenario: A doctor is about to start a patient on a drug that has a REMS. The prescriber does not realize that the drug has a REMS. Fortunately, the prescriber’s EHR contains SPL data.

• Using the <stakeholder> data element, the EHR notifies the prescriber that they have a role to play in the REMS.

• Using the <protocol> and <requirement> data elements, the EHR notifies the prescriber that there are several steps they have to take when initiating therapy with the patient, including providing the patient with counseling materials.

• Using the <documentReference> data element, the EHR presents a copy of the counseling material to the prescriber to print and give to the patient.
Use of SPL in the Healthcare System: Dispenser Example

Scenario: A pharmacist is about to fill a prescription for a drug with a REMS. The pharmacist is aware that a REMS exists for the drug, but is not aware that the REMS has recently changed. Fortunately, the pharmacist’s pharmacy system contains SPL data.

- Using the `<protocol>` and `<requirement>` data elements, the pharmacy system notifies the pharmacist that they must now confirm that a specific lab test result is on file before dispensing the drug.

- Using the `<documentReference>` data element, the pharmacy system learns that the lab test results can be requested electronically.

- Thanks to the “trigger” provided by SPL, the pharmacy system can now, using a different data standard, check with the REMS program to determine whether there is a negative lab test on file.
Next Steps

• Sponsors are now able to submit their REMS in SPL format.

• Once REMS SPL files are approved, they will be made available on DailyMed

• We will be available at FDAREMSWebsite@fda.hhs.gov to help REMS SPL submitters with their submissions.

• We are preparing a draft guidance under FD&C 745A(a) that would require REMS submissions in SPL format.
  – Electronic submission requirements take effect 2 years from the publishing of a final guidance.
  – We will continue to have opportunities for stakeholder feedback prior to issuing final guidance.
Information For Industry

Click for:

- REMS@FDA
- REMS Integration Initiative
- Structured Product Labeling Resources Website
- Submitting REMS in SPL Format (Webinar)
- DailyMed (Future home of REMS SPL Data Files)
- PDF of the slides for today’s sessions
- If we did not get to you question, you can always email to us at:
  
  **CDERSBIA@fda.hhs.gov**

Open Q&A begins shortly – type in your questions now.

**Click Here for Evaluation and Certificate**

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