SBIA Webinar:
Introduction to REMS SPL

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FDA | CDER
August 24th, 2016
Agenda

1. **Background**

2. How REMS SPL is Structured

3. How to Create REMS SPL

4. How to Submit REMS SPL to FDA

5. Next Steps
What are REMS?

- REMS are programs designed to help ensure that drugs with serious risks are used safely.
- REMS with Elements to Assure Safe Use (ETASU) place certain requirements on healthcare providers and patients to make sure the drug is used safely.
- A number of parties play a role in REMS design and implementation:

<table>
<thead>
<tr>
<th>Document &amp; Design</th>
<th>Review &amp; Approve</th>
<th>Implement</th>
<th>Adopt</th>
<th>Assess</th>
<th>Review &amp; Modify</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>FDA</td>
<td>Sponsor</td>
<td>Distributors</td>
<td>Sponsor</td>
<td>FDA</td>
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<td></td>
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<td>Dispensers</td>
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<td>Institutions</td>
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<td></td>
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<td>Prescribers</td>
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<td></td>
<td></td>
<td></td>
<td>Patients</td>
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</tbody>
</table>
Approved REMS

As of August 2016, there were 75 approved REMS, which addressed 150+ distinct applications.

42 of those 75 REMS have ETASU.

Source: REMS@FDA  http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
REMS 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.
Yet there is little standardization of how REMS processes 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
- It’s not always easy to find information on what is expected of healthcare providers and patients
Proposal: Capture REMS in SPL Format

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 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.
Why Standardize REMS via SPL?

• SPL is well-equipped to capture REMS information

• SPL unites REMS information with other relevant product information

• Using SPL lets us leverage existing data standards process and infrastructure
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REMS SPL starts with the official “REMS Document”

REMS Document

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
   thrombocytopenia and safety-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 201.24.
   The Adempas Medication Guide is part of the REMS and is appended.

B. Elements to Assess 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

Prescriber Enrollment and Agreement Form
## 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>
REMS documents are transformed into REMS Summaries

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

- 3. Pharmacies that dispense Drug X:
  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 processes 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:
  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 processes and procedures to verify dispensing to certified infusion centers only.
  5. Enroll in the REMS by completing and submitting the Pharmacy Enrollment Form.
REMS Summaries are then transformed into standardized data elements.
Example of codified REMS within SPL

- **When:** While prescribing (C0P03)
- **What:** Counsel patient (C0R002)
- **Who:** Prescriber (C0SH01)
- **Using 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></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>
REMS SPL information is shared across the healthcare system

SPL data is transmitted from the sponsor to patients, healthcare providers, and the public.
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Process for creating REMS SPL was informed by a pilot with sponsors

Pilot was announced in FR and launched in October 2015, and ended in May 2016. 9 sponsors participated in the pilot.

General pilot process:

1. Pilot Materials distributed to sponsors.
2. Sponsors developed REMS SPL submissions using materials.
3. Sponsors shared SPL files with FDA.
4. FDA and sponsors discussed findings.
5. FDA revised materials to address sponsor concerns

Pilot helped us refine the materials and instructions and learn more about the process of capturing REMS in SPL format.
Steps to creating REMS SPL

Steps to successful REMS SPL development:

1. Assemble team of REMS Experts and SPL Experts

2. Review FDA-Provided Materials

3. Codify REMS in SPL Format
   - Code REMS Document and basic product information
   - Create and code the REMS Summary
   - Code the REMS Data Elements to the summary
Assemble Team of REMS and SPL Experts

REMS Experts
Subject matter experts in the REMS.
• Develop REMS Summary
• Identify relevant data elements for each summary item and work with SPL Experts

SPL Experts
Experts in SPL and XML coding.
• Code REMS Document
• Code REMS Summary developed by REMS experts
• Code REMS data elements in collaboration with REMS Experts.
Review FDA-Provided Materials

- Technical instructions for producing SPL files, including REMS SPL
- Includes relevant information for both REMS experts and SPL experts

Implementation Guide

- Terminology for REMS Data Elements
- Describes REMS requirements, timings (protocol), and participants (stakeholder)
Review FDA-Provided Materials

- Tool to facilitate creation of SPL documents
- Use of this is not required; Some SPL developers prefer to use their own tools

XForms

- Example of successfully completed REMS SPL
- Can be used to see how REMS Document, Summary, and Data Elements work together

Sample REMS SPL File
Code REMS Document: Sections

REMS SPL has standardized section headers placed around the REMS Document text.

```xml
<component>
    <section ID="ID_39e342b0-4447-4a2a-83b1-7724f9e68c0d">
        <id root="6f9cb370-5c0d-4f78-8712-b8627153bd9c"/>
        <code code="X1111-1" codeSystem="2.16.840.1.113883.6.1" displayName="REMS Goals"/>
        <title>I. GOALS</title>
        <content styleCode="italics">Insert REMS Goals Text Here</content>
        <effectiveTime value="20160824"/>
    </section>
</component>
```
Code REMS Document: Link to Label

REMS SPL includes a link to relevant labels.

For certain REMS, including shared system REMS submitted under a DMF, there may be links to multiple labels.

```xml
<relatedDocument typeCode="XCRPT">
  <relatedDocument>
    <setId root="12345678-9abc-def-1234-56789abc"/>
  </relatedDocument>
</relatedDocument>
```
REMS SPL also includes some background about the product (but with less detail than the labeling SPL)

```xml
<section>
  <id root="24d8b579-6d31-4ead-a915-726b1520558d"/>
  <code code="48780-1" codeSystem="2.16.840.1.113883.6.1" displayName="SPL PRODUCT DATA ELEMENTS SECTION"/>
  <effectiveTime value="20130403"/>
  <subject>
    <manufacturedProduct>
      <manufacturedProduct>
        <name>[Brand Name of Drug or name of REMS Class]</name>
      </manufacturedProduct>
    </subjectOf>
    <approval>
      <id extension="[application_number]" root="2.16.840.1.113883.3.150"/>
      <code code="c73594" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="[application_type]"/>
      <author>
        <territorialAuthority>
          <territory>
            <code code="USA" codeSystem="2.16.840.1.113883.5.28"/>
          </territory>
        </territorialAuthority>
      </author>
    </approval>
  </subjectOf>
</manufacturedProduct>
</subject>
</section>
```
Create and Code REMS Summary

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

1. Healthcare Providers who prescribe drug X must:

<table>
<thead>
<tr>
<th>To become certified to prescribe</th>
<th>1. Review the drug’s Prescribing Information.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Enroll in the REMS by completing the Drug X REMS Enrollment Form and submitting it to the REMS Program.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before treatment initiation (first dose)</th>
<th>3. Counsel the patient using Drug X REMS Counseling Material.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4. Assess the patient’s [condition(s) or health status(es)].</td>
</tr>
</tbody>
</table>

REMS Summaries will have multiple tables: one for each participant in the REMS.
Create and Code REMS Summary

The Summary includes

• Actions taken by a REMS stakeholder (e.g. healthcare provider or patient)
• Requirements explicitly stated in the REMS document.

The Summary does not include

• Requirements mentioned in other REMS materials, such as the Supporting Document, training materials, or enrollment forms
• Activities that REMS participants learn about or acknowledge but do not agree to undertake.
• Activities that REMS participants do not need to complete in order to be able to use the drug.
Create and Code REMS Summary

The language in the REMS Summary is short and succinct.

- Summary items are generally 1-2 sentences long and do not use too much detail.
- Summary generally avoid complex formatting, such as bulleted and indentation, since certain downstream users of REMS SPL may not support this type of formatting.
- FDA’s sample REMS SPL provides language that is applicable to most REMS and can help facilitate consistency across REMS.
Code REMS Data Elements

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)].

<stakeholder>

<protocol>

<requirement>

<document Reference>
Code 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)
Code 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.
Code 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
Code 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.
Review of REMS SPL Creation

2. Transform REMS Documents into Summaries
3. Map Summaries to Data Elements (e.g., using spreadsheet)

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

To be able to prescribe

Enroll in REMS

Standardized Data Elements

Stakeholder: Prescribers

Protocol

Requirement
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Requesting REMS Summaries

FDA will accept REMS documents in SPL format starting on Friday, September 2nd

To facilitate consistent and high-quality REMS SPL submissions, FDA will provide submitters with FDA-developed REMS summaries that they may use in creating their REMS SPL documents.

- FDA will provide these summaries for 1 year.
- If you would like a summary, please request one from the REMS Website team.
How to Submit REMS to FDA in SPL format: new/modified REMS

If you are submitting a new application or modifying an existing REMS and wish to submit the REMS in SPL format:

1. As soon as you know your intent to submit in SPL format, reach out to the REMS Website team at FDAREMSWebsite@fda.hhs.gov
2. Submit your REMS SPL through the gateway in eCTD format as described on a subsequent slide. (Also continue to submit your REMS in .doc format to facilitate negotiation with the review team.)
3. If desired, request a REMS Summary from the REMS Website team. For new/modified REMS, the team will provide a summary within 3 business days of approval.
4. Within 14 days of approval, submit final SPL to eList.
5. Address any changes with the REMS Website team to prepare for publication to DailyMed and REMS@FDA.

August 24, 2016
Submitting REMS SPL as part of the eCTD

For REMS SPL submitted as part of a new application/modification

The REMS SPL file should be named rem-spl-[optional xyz].xml and placed in a folder named “spl” under the appropriate folder for REMS in module 1, as shown in the example below:

\NDA12345\0001\m1\us\116-risk-mgt\spl\rems-spl-final.xml

The REMS SPL file should be referenced in the eCTD xml backbone under section 1.16.
How to Submit REMS to FDA in SPL format: already-approved REMS

If you wish to convert an already-approved REMS to SPL format:

1. As soon as you know your intent to submit in SPL format, reach out to the REMS Website team at FDAREMSSebsite@fda.hhs.gov

2. If desired, request a REMS Summary from the REMS Website team.

3. Once REMS SPL is prepared, submit it to eList.

4. Address any changes with the REMS Website team to prepare for publication to DailyMed and REMS@FDA.
How to Submit REMS to FDA in SPL format: shared-system REMS

If you are submitting SPL for a drug that is part of a shared system follow the procedures outlined in the previous slides, but with the following additions:

- We cannot accept REMS SPL from individual shared system members; all members should participate together.
- If shared system sponsors submit their REMS separately, the REMS SPL for each should be identical with the exception of the product and \(<\text{relatedDocument}>\) information.
- If shared system sponsors submit REMS under a single DMF, the SPL document’s product and \(<\text{relatedDocument}>\) information should reference all products in the system.

FDA will provide an indexing file that identifies the drugs in each shared system REMS.
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Next Steps

- 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.
Final Thoughts: 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
Final thoughts: SPL in the healthcare system

SPL can also play a major role in standardizing and integrating REMS as part of the “Common REMS Platform”
Resources

Click for:

- **Structured Product Labeling (SPL) Implementation Guide with Validation Procedures**
- **The FDA’s REMS Integration Initiative**
- **PDF of these presentation slides**
- **REMS SPL Support: FDAREMSWebsite@fda.hhs.gov**

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

*Click for Evaluation and Certificate*