'REMS in Structured Product Labeling Format: An Introduction

Adam Kroetsch

FDA | CDER
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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:
## What REMS SPL Looks Like

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

<table>
<thead>
<tr>
<th>To become certified to prescribe</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Be able to [clinical activity to be performed].</td>
</tr>
<tr>
<td></td>
<td>2. Review the drug’s Prescribing Information.</td>
</tr>
<tr>
<td></td>
<td>3. Review the following: [List of Prescriber Educational Material(s)].</td>
</tr>
<tr>
<td></td>
<td>4. Receive training provided by [entity providing the training, e.g. the applicant, a CE provider].</td>
</tr>
<tr>
<td></td>
<td>5. Successfully complete the [Knowledge Assessment Form] and submit it to the REMS Program.</td>
</tr>
<tr>
<td></td>
<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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7. Counsel the patient on [topic]</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Counsel the patient using [REMS material].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Counsel the patient on [topic] using [REMS material].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Provide the patient with the [REMS Material].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Assess the patient’s [condition(s) or health status(es)].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Assess the patient’s [condition(s) or health status(es)] Document and submit the results to the REMS Program using [REMS Material(s)].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Assess the patient’s [condition or health status] by [list of lab test(s) or monitoring].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Assess the patient’s [condition(s) or health status(es)] by [list of lab test(s) or monitoring]. Document and submit the results to the REMS Program using [REMS Material(s)].</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Complete the [Patient Form]. Provide a completed copy of the form to the patient.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Complete the [Patient Form]. Retain a completed copy in the patient’s record.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Complete the [Patient Form]. Provide a completed copy of the form to the patient and retain a copy in the patient’s record.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Enroll the patient by completing and submitting the [Patient Enrollment Form] to the REMS program.</td>
</tr>
</tbody>
</table>
1. Healthcare Providers who prescribe [drug/class name] must:

<table>
<thead>
<tr>
<th>Content ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>R001</td>
<td>Be able to [clinical activity to be performed].</td>
</tr>
<tr>
<td>R002</td>
<td>Review the drug’s Prescribing Information.</td>
</tr>
<tr>
<td>R003</td>
<td>Review the following: [List of Prescriber Educational Material(s)]</td>
</tr>
<tr>
<td>R004</td>
<td>Receive training provided by [entity providing the training, e.g.</td>
</tr>
<tr>
<td>R005</td>
<td>Successfully complete the [Knowledge Assessment Form] and submit</td>
</tr>
<tr>
<td>R006</td>
<td>Enroll in the REMS by completing the [Enrollment Form] and submit</td>
</tr>
</tbody>
</table>

Before treatment initiation (first dose)
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

<table>
<thead>
<tr>
<th>Prescribers must:</th>
<th>Dispensers must:</th>
<th>Distributors must:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete training.</td>
<td>• Complete training.</td>
<td>• Check to make sure dispensers are “certified to dispense” before shipping the drug.</td>
</tr>
<tr>
<td>• Complete an enrollment form, thereby becoming “certified” to prescribe.</td>
<td>• Complete an enrollment form, thereby becoming “certified” to dispense.</td>
<td></td>
</tr>
<tr>
<td>• Counsel and educate patients.</td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>• Make sure patients agree to participate in the REMS and enroll them if necessary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Assess or monitor patients to make sure “safe use conditions” are present</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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**

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.
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 processes 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:

---

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)].

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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>Drug Name, NDA number, dosage form</th>
<th>Approval Date</th>
<th>REMS Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adasuve (loxapine), aerosol, powder</strong>&lt;br&gt;NDA #022549</td>
<td>10/19/2016</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Addyi (flibanserin), tablet</strong>&lt;br&gt;NDA #022526</td>
<td>05/10/2016</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Adempas (riociguat), tablet, film coated</strong>&lt;br&gt;NDA #204819</td>
<td>01/17/2017</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Afrozza (insulin human), powder, metered</strong>&lt;br&gt;NDA #022472</td>
<td>04/01/2016</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Alosetron</strong>&lt;br&gt;Shared System REMS</td>
<td>11/22/2016</td>
<td>✓</td>
</tr>
</tbody>
</table>
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

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

### Standardized Data Elements

- **Stakeholder**: Prescribers
- **Protocol**: To be able to prescribe
- **Requirement**: Enroll in REMS
REMS Summary

**<stakeholder>**

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

**<protocol>**

**<requirement>**

**<document Reference>**
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></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
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**

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