CDER SBIA Webinar Series

SBIA Webinar: Introduction to REMS SPL

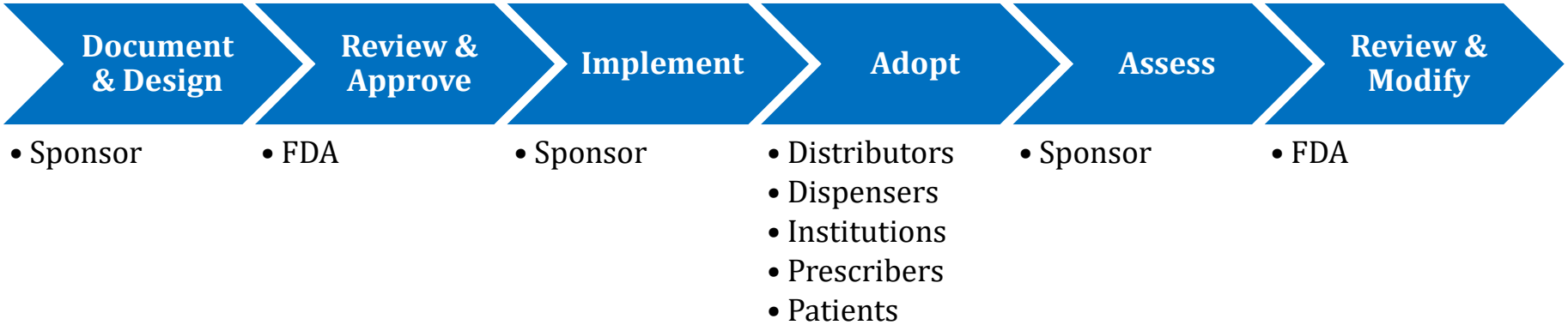
Adam Kroetsch and **Aaron Sherman**
FDA | CDER
August 24th, 2016

Agenda

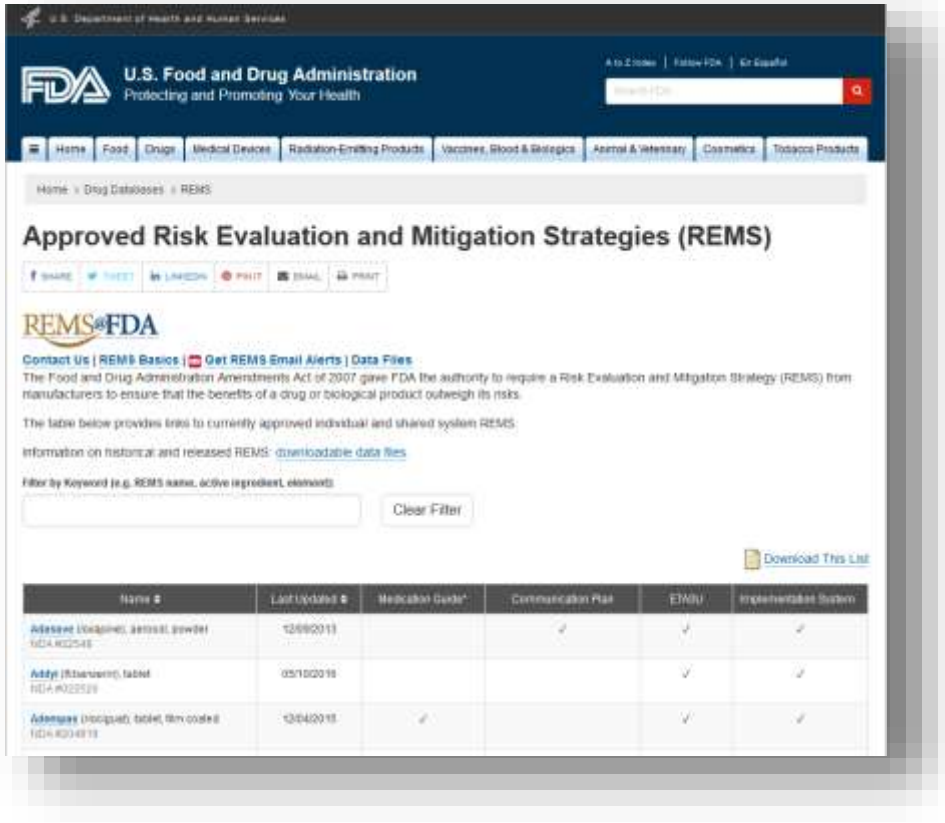
1. **Background**
2. How REMS SPL is Structured
3. How to Create REMS SPL
4. How to Submit REMS SPL to FDA
5. Next Steps

What are REMS?

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



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 from, 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:

- F SPL stands for "Structured Product Labeling" but covers product information beyond labeling
- F 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?

- F SPL is well-equipped to capture REMS information
- F SPL unites REMS information with other relevant product information
- F 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

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


Adempas REMS (Risk Evaluation and Mitigation Strategy)

Prescriber Enrollment and Agreement Form

REMS SPL captures the "4 W's" of REMS

Data Element	Description	Examples
Stakeholder ("Who")	The party that must meet the REMS requirement	prescriber, dispenser, health care setting
Protocol ("When")	A particular "stage" in the treatment process around which REMS activities may occur	certification, prescribing, dispensing, administration
Requirement ("What")	A clinical or administrative activity that must be performed as part of the REMS	counseling a patient, completing an enrollment form, lab testing
Material reference ("With What")	Reference to approved REMS material with which the requirement is carried out	enrollment form, medication guide, educational pamphlet

REMS documents are transformed into REMS Summaries

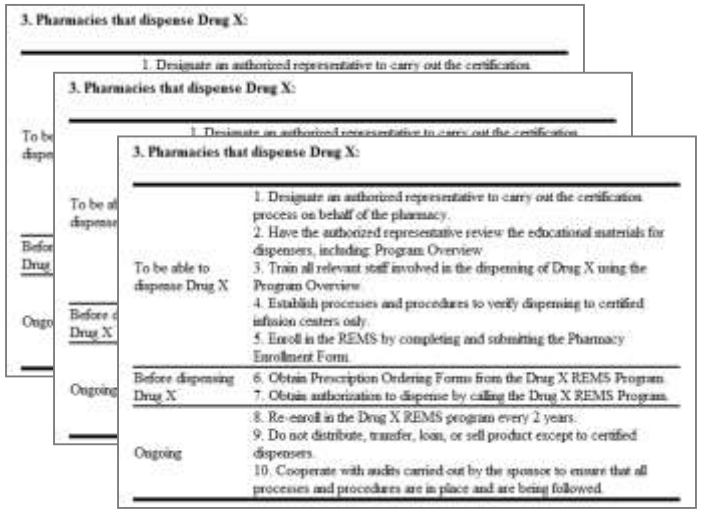
REMS Document Text

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



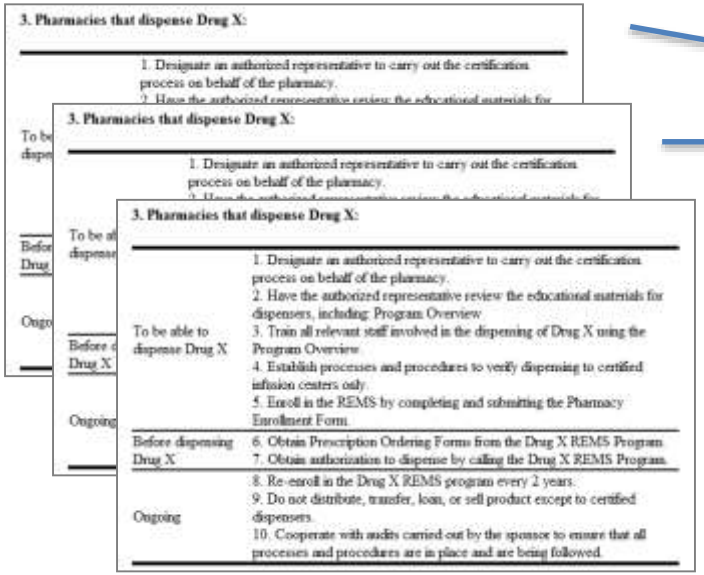
3. Pharmacies that dispense Drug X:

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.

To be able to dispense Drug X	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.
Before dispensing Drug X	6. Obtain Prescription Ordering Forms from the Drug X REMS Program. 7. Obtain authorization to dispense by calling the Drug X REMS Program.
Ongoing	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 Summaries are then transformed into standardized data elements

REMS Summaries



Standardized Data Elements

Stakeholder	Prescribers
Protocol	To be able to prescribe
Requirement	Enroll in REMS

Example of codified REMS within SPL

```
<protocol>
    <code code="C0P03" codeSystem="2.16.840.1.113883.3.26.1.1"
    <component>
        <sequenceNumber value="1"/>
        <requirement>
            <code code="C0R002" displayName="Counsel patient"
                <originalText>
                    <reference value="#A005"/>
                </originalText>
            </code>
            <participation typeCode="PPRF">
                <stakeholder>
                    <code code="C0SH01" displayName="prescribe
                </stakeholder>
            </participation>
            <subject>
                <documentReference>
                    <id root="00000000-0000-0000-0000-00000000
                        <!-- Document reference links to docum
                    </id>
                </documentReference>
            </subject>
        </requirement>
    </component>
```

When:
- While prescribing (C0P03)

What:
- Counsel patient (C0R002)

Who:
- Prescriber (C0SH01)

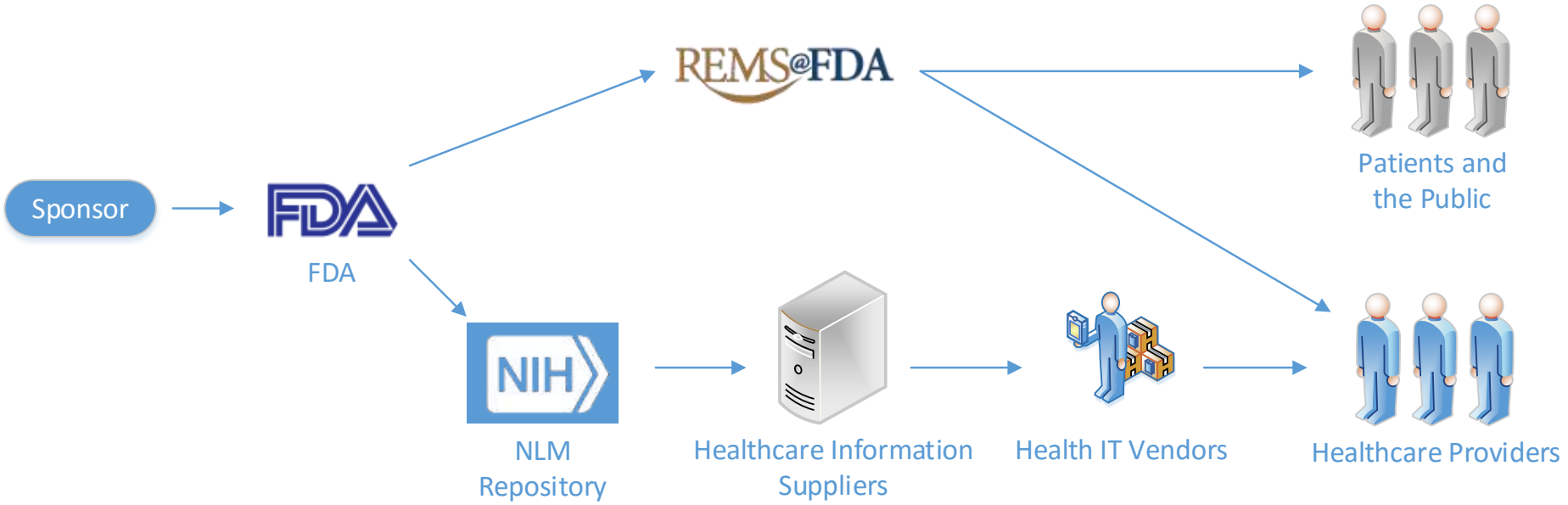
Using What:
- documentReference

Codified REMS SPL information can be displayed in many different ways

Before/During/After	Activity	Stakeholder	Requirement	Document
before	all activity	dispenser	designate authorized representative	
before	all activity	dispenser	Have representative review educational materials	Program Overview
before	all activity	dispenser	train staff	Program Overview
before	all activity	dispenser	Establish processes and procedures to verify safe use conditions	
before	all activity	dispenser	Enroll in REMS	Pharmacy Enrollment Form
before	dispensing	dispenser	obtain dispensing authorization	
every 2 years during	dispensing	dispenser	Enroll in REMS	
during	dispensing	dispenser	ensure dispensing only to certified provider	
during	dispensing	dispenser	Cooperate with audits	

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.

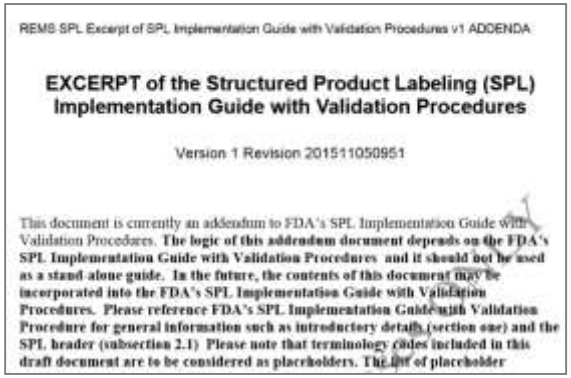
- F Develop REMS Summary
- F Identify relevant data elements for each summary item and work with SPL Experts

SPL Experts

Experts in SPL and XML coding.

- F Code REMS Document
- F Code REMS Summary developed by REMS experts
- F Code REMS data elements in collaboration with REMS Experts.

Review FDA-Provided Materials


REMS SPL Excerpt of SPL Implementation Guide with Validation Procedures v1 ADDENDA

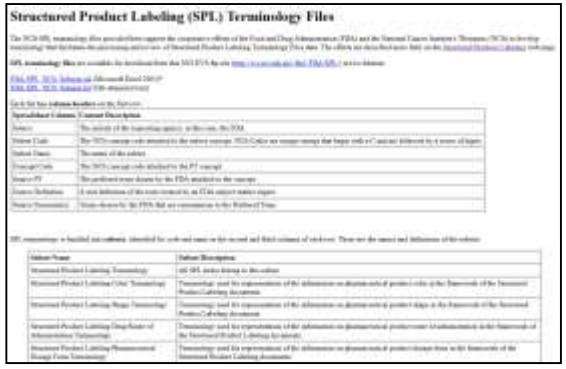
EXCERPT of the Structured Product Labeling (SPL) Implementation Guide with Validation Procedures

Version 1 Revision 201511050951

This document is currently an addendum to FDA's SPL Implementation Guide with Validation Procedures. **The logic of this addendum document depends on the FDA's SPL Implementation Guide with Validation Procedures and it should not be used as a stand-alone guide. In the future, the contents of this document may be incorporated into the FDA's SPL Implementation Guide with Validation Procedures. Please reference FDA's SPL Implementation Guide with Validation Procedure for general information such as introductory details (section one) and the SPL header (subsection 2.1) Please note that terminology codes included in this draft document are to be considered as placeholders. The list of placeholder**

Implementation Guide

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


Structured Product Labeling (SPL) Terminology Files

NCI Terminology

- F Terminology for REMS Data Elements
- F Describes REMS requirements, timings (protocol), and participants (stakeholder)

Review FDA-Provided Materials

XForms

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

Sample REMS SPL File

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

Code REMS Document: Sections

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

```
<component>
    <section ID="ID_39e342b0-4447-4a2a-83b1-7724f9e68ccd">
        <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<content styleCode="italics"> </content>
        </title>
        <text>
            <paragraph>Insert REMS Goals Text Here
            </paragraph>
        </text>
        <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.

```
<relatedDocument typeCode="XCRPT">
    <relatedDocument>
        <setId root="12345678-9abc-def-1234-56789abc"/>
    </relatedDocument>
</relatedDocument>
```

Code REMS Document: Product Info

REMS SPL also includes some background about the product (but with less detail than the labeling SPL)

```
<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:

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 Summaries will have multiple tables: one for each participant in the REMS.

Create and Code REMS Summary

The Summary includes

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

The Summary does not include

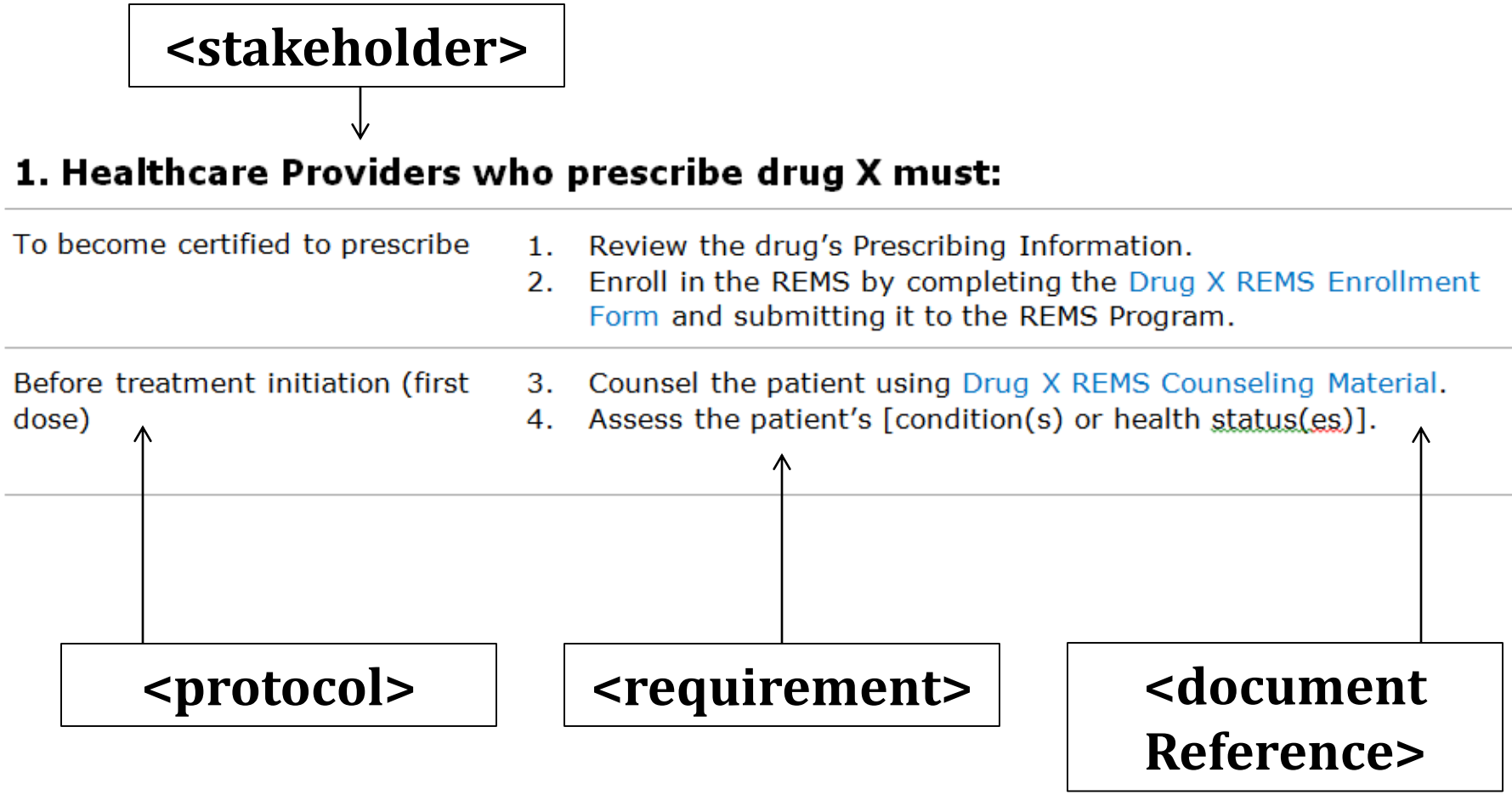
- F Requirements mentioned in other REMS materials, such as the Supporting Document, training materials, or enrollment forms
- F Activities that REMS participants learn about or acknowledge but do not agree to undertake.
- F Activities that REMS participants do not need to complete in order to be able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

Create and Code REMS Summary

The language in the REMS Summary is short and succinct.

- F Summary items are generally 1-2 sentences long and do not use too much detail.
- F Summary generally avoid complex formatting, such as bulleting 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



Code REMS Data Elements

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

- F Prescriber
- F Dispenser
- F Patient
- F Distributor
- F 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

1. Code REMS Document and related product information
2. Transform REMS Documents into Summaries
3. Map Summaries to Data Elements (e.g., using spreadsheet)

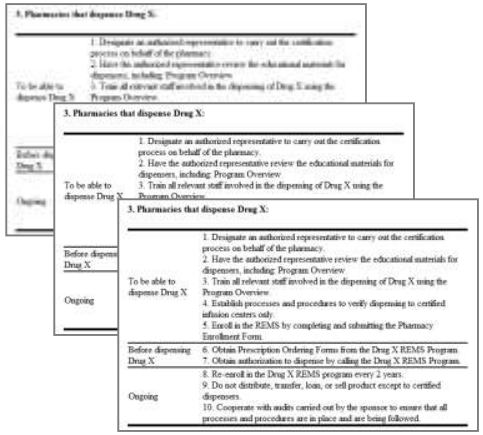
REMS Document Text

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



Standardized Data Elements

Stakeholder	Prescribers
Protocol	To be able to prescribe
Requirement	Enroll in REMS

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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.

- F FDA will provide these summaries for 1 year.
- F 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

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

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.

Submitting REMS SPL as part of the eCTD

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

The REMS SPL file should be named rems-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 FDAREMSWebsite@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:

- F We cannot accept REMS SPL from individual shared system members; all members should participate together.
- F If shared system sponsors submit their REMS separately, the REMS SPL for each should be identical with the exception of the product and <relatedDocument> information.
- F If shared system sponsors submit REMS under a single DMF, the SPL document's product and <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

TABLE 2 Standard Operating Procedures (SOPs)*

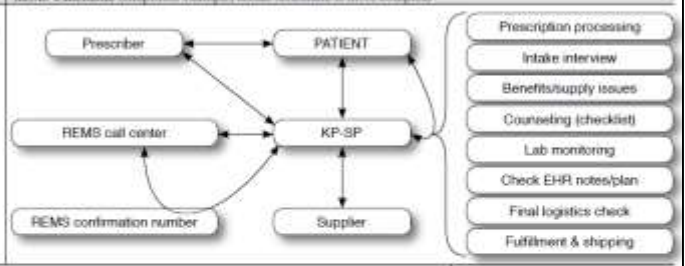
KP-SP Policy and Procedure for Dispensing <GENERIC NAME> <BRAND NAME>

Scope	Purpose
Example: "This process will be used to ensure the proper administration of and compliance with the FDA-approved REMS for <Drug X> with the Kaiser Permanente Specialty Pharmacy…."	Example: "To describe the proper procedures for prescription intake, REMS Elements To Assure Safe Use, added safety monitoring, and efficient delivery of clinical and dispensing services for <Drug X>…."
KP-SP Contact Information and Business Hours	**Definitions**
• Phone/Fax/TTY numbers • E-mail address • Business hours	Example: For "PIMS," "SPIMS," and other acronyms and system names used in the SOP.

REMS Overview

- Medication guide
- Communication plan participation
- Elements to ensure safe use
- Implementation system
- Assessment-possible participation

REMS Schematic (simplified example; actual schematic is more complex)



SP Processes Step-By-Step (Quasi-Based Process)	REMS Contact Information
Example: 1. Review incoming Rx* or refill requirements* 2. Check labs/tests, EHR notes, MD visits/notes, Rx profile, etc.* 3. Counsel patient/caregiver* and review benefits issues 4. Adverse event documentation requirements 5. Obtain confirmation number from REMS hub 6. Dispensing elements* 7. Documentation requirements* logistics, labels, filling, shipping 8. REMS data transmission requirements* 9. Perform drug accountability procedures * with detailed checklist(s); all steps documented	Example: Call center numbers, online elements, locations for forms, etc. **REMS Data Requirement** Example: What information is required for call center; what data are transmitted electronically; PHI safeguards; inventory reporting requirements, etc.

Metrics	Clinical Monitoring Specifications
Standards for measurement of processes, adherence, intermediary clinical indicators, or outcomes	Labs, pregnancy testing, EKGs, etc.
References	**Usage Management Criteria, Guidelines, or Initiatives**
Example: Internal (evidence reviews, formulary decisions, guidelines); external (critical FDA documents, manufacturer resources, REMS)	Example: Guidelines defining safety monitoring; initiatives to review treatment alternatives; criteria for treatment review after a specified duration of therapy; etc.

KP-SP Policy and Procedure for <generic name> (DATE)

*For each drug handled through KP-SP, a SOP is developed to define processes. This SOP also supports the development of an SPIMS module for the drug and can be used for decentralized clinical monitoring services coordinated with the internal SP. This table shows the possible elements of the SOP.

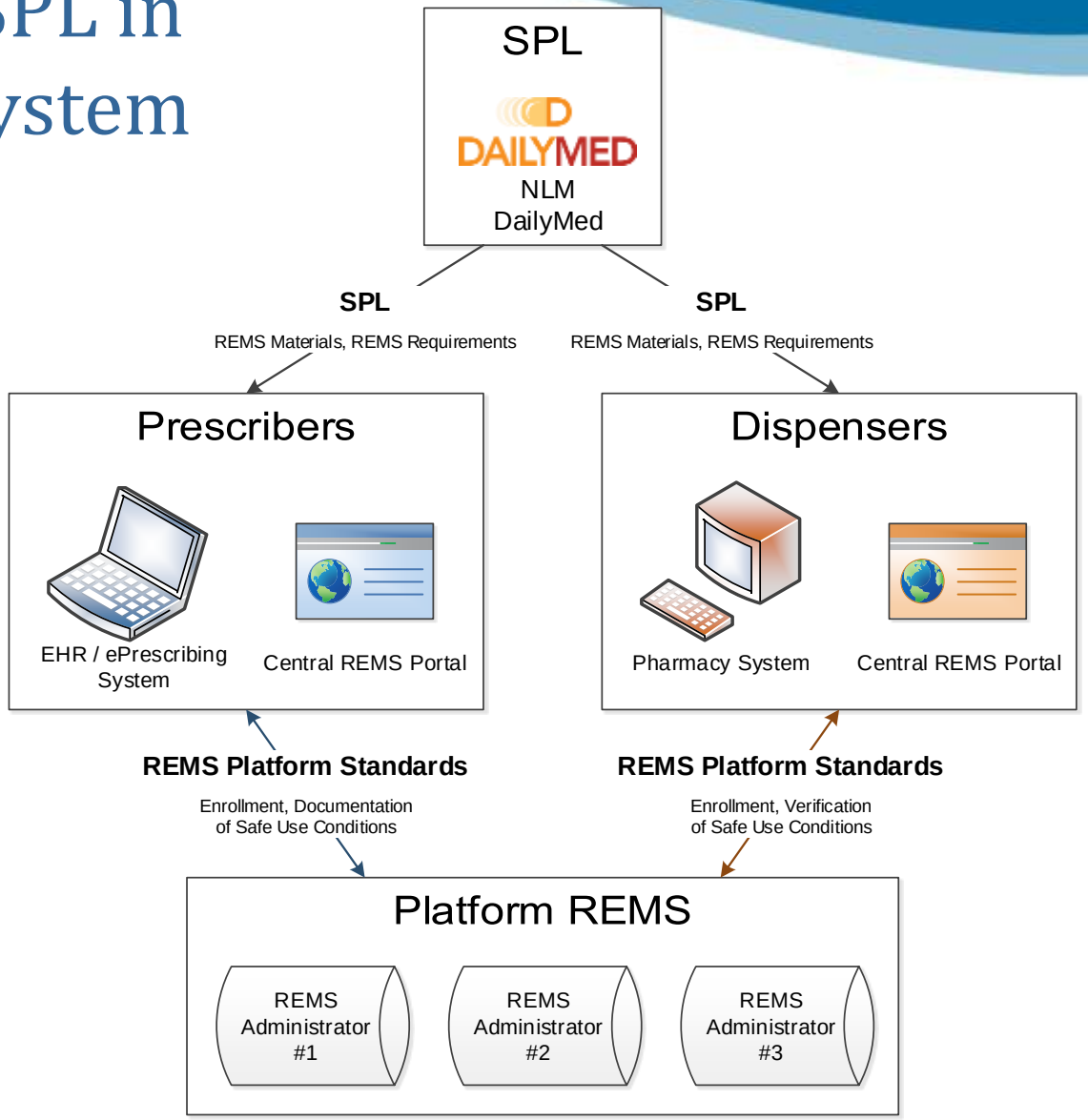
EHR = electronic health record; EKG = electrocardiogram; FDA = U.S. Food and Drug Administration; KS-SP = Kaiser Permanente Specialty Pharmacy; MD = medical doctor; PHI = protected health information; PIMS = Pharmacy Information Management System; REMS = Risk Evaluation and Mitigation Strategies; Rx = prescription; SP = specialty pharmacy; SPIMS = Specialty Pharmacy Information Management System; TTY = text telephone device.

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:

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

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

Click for Evaluation and Certificate