CDER SBIA Webinar Series

U.S. FOOD & DRUG ADMINISTRATION

REMS in Structured Product Labeling Format: An Introduction

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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:

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.

Access this form online at www.adempasREMS.com, fax this form to 1-855-662-5200 or call the Adempas REMS Program at 1-855-4ADEMPAS (1-855-423-3672).

Prescriber Information (* indicates required field)

First Name*: | Middle Initial: | Last Name*: | NPI*:

Specialty*: ☐ Cardiology ☐ Pulmonology ☐ Other | Credentials*: ☐ MD ☐ DO ☐ NP ☐ PA ☐ Other with prescriptive authority

Practice/Facility Name:

Address Line 1*: | Address Line 2:

City*: | State*: | Zip code*:

Phone*: | Fax*: | Email*: | Preferred Method of Contact: ☐ Phone ☐ Email ☐ Fax

Office Contact

First Name: | Last Name: | Email* (required if Office Contact is provided):

Prescriber REMS Agreement

By signing below, you signify your understanding of the risks of Adempas treatment and your obligation as an Adempas prescriber to educate your female patients about the Adempas REMS Program, monitor them appropriately, and report any pregnancies to the Adempas REMS Program. Specifically, you attest to the following:

- I have read the *Adempas Full Prescribing Information, Adempas Medication Guide* and the *Prescriber Guide for the Adempas REMS Program*.
- I agree to enroll all female patients into the Adempas REMS Program.
- I will:
  - determine the reproductive potential status of all female patients using the definitions provided in the *Prescriber Guide for the Adempas REMS Program*.
  - advise all females that Adempas is only available through a restricted distribution program called the Adempas REMS Program.
  - counsel Females of Reproductive Potential (FRP) on Adempas risks, including serious birth defects, and review the *Adempas Medication Guide* and the *Adempas REMS Guide for Females Who Can Get Pregnant* with the patient.
  - counsel each FRP to immediately contact her healthcare provider if she misses a menstrual period or suspects pregnancy.
  - counsel the Pre-Pubertal Female (PPF) patient and/or her parent/guardian on the Adempas risks, including serious birth defects, and review the *Adempas Medication Guide* with the patient and parent/guardian.
  - verify the reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older.
  - counsel the PPF patient and/or her parent/guardian to contact her healthcare provider if she begins her menstrual period.
  - order and review pregnancy tests for FRPs prior to initiating Adempas treatment, monthly during treatment, and for one month after stopping treatment.
  - counsel each FRP to use reliable contraception during Adempas treatment, and for one month after stopping treatment, and discuss her medical options in the event of unprotected sexual intercourse or known or suspected contraceptive failure.
  - report any change in reproductive status by submitting an *Adempas REMS Reproductive Potential Status Form* within 10 business days of becoming aware of the change.
  - counsel female patients who fail to comply with the Adempas REMS Program requirements.
  - notify Bayer of any pregnancies at 1-888-842-2937 or send the information to DrugSafety.GPV.US@bayer.com.

REQUIRED | Prescriber Signature*: | Date* (MM/DD/YYYY):

To report any adverse events, product technical complaints, medication errors or pregnancies associated with the use of Adempas, contact Bayer at 1-888-842-2937, or send the information to DrugSafety.GPV.US@bayer.com.

Adempas riociguat tablets

Phone: 1-855-4ADEMPAS (1-855-423-3672) www.adempasREMS.com Fax: 1-855-662-5200

Reference ID: 3522688

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What REMS SPL Looks Like

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

To become certified to prescribe	1. Be able to [clinical activity to be performed]. 2. Review the drug's Prescribing Information. 3. Review the following: [List of Prescriber Educational Material(s)]. 4. Receive training provided by [entity providing the training, e.g. the applicant, a CE provider]. 5. Successfully complete the [Knowledge Assessment Form] and submit it to the REMS Program. 6. Enroll in the REMS by completing the [Enrollment Form] and submitting it to the REMS Program.
Before treatment initiation (first dose)	7. Counsel the patient on [topic] OR Counsel the patient using [REMS material]. OR Counsel the patient on [topic] using [REMS material]. 8. Provide the patient with the [REMS Material]. 9. Assess the patient's [condition(s) or health status(es)]. OR Assess the patient's [condition(s) or health status(es)]. Document and submit the results to the REMS Program using [REMS Material(s)]. OR Assess the patient's [condition or health status] by [list of lab test(s) or monitoring]. OR 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)]. 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. OR Complete the [Patient Form]. Provide a completed copy of the form to the patient and retain a copy in the patient's record. 11. Enroll the patient by completing and submitting the [Patient Enrollment Form] to the REMS program. OR

What REMS SPL Really Looks Like

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                <tbody>
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                        <td styleCode="Botrule">To become certified to prescribe</td>
                        <td styleCode="Botrule">
                            <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)
                            <br/>
                            <content ID="R004">4.   Receive training provided by [entity providing the training, e.g.
                            <br/>
                            <content ID="R005">5.   Successfully complete the [Knowledge Assessment Form] and submit
                            <br/>
                            <content ID="R006">6.   Enroll in the REMS by completing the [Enrollment Form] and submit
                        </td>
                    </tr>
                    <tr>
                        <td styleCode="Botrule">Before treatment initiation (first dose)</td>
```

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 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.

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

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

Using these “4 W’s”, REMS documents are transformed into REMS Summaries

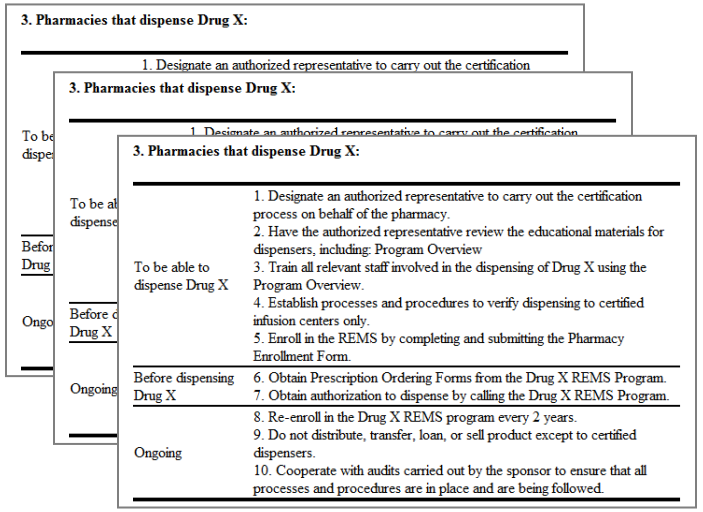
REMS Document Text

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:

To be able to 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.
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 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 have multiple tables: one for each participant in the REMS.

Why SPL?

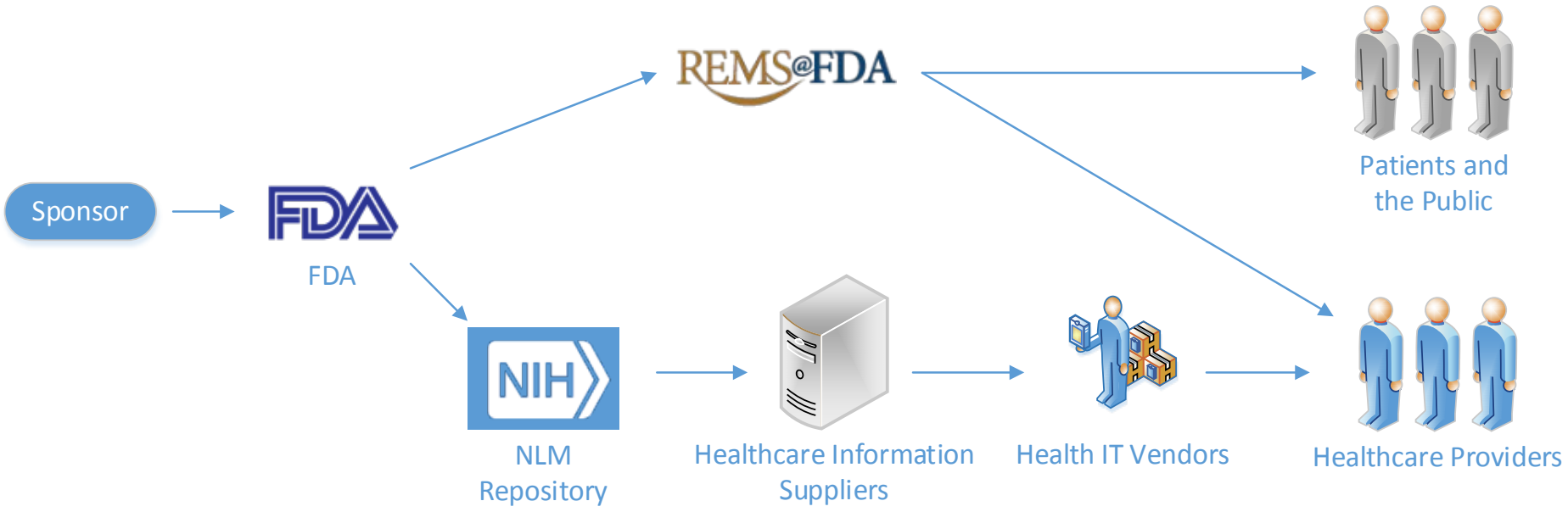
1. Makes REMS information easier to understand.

2. **Makes REMS information more accessible.**

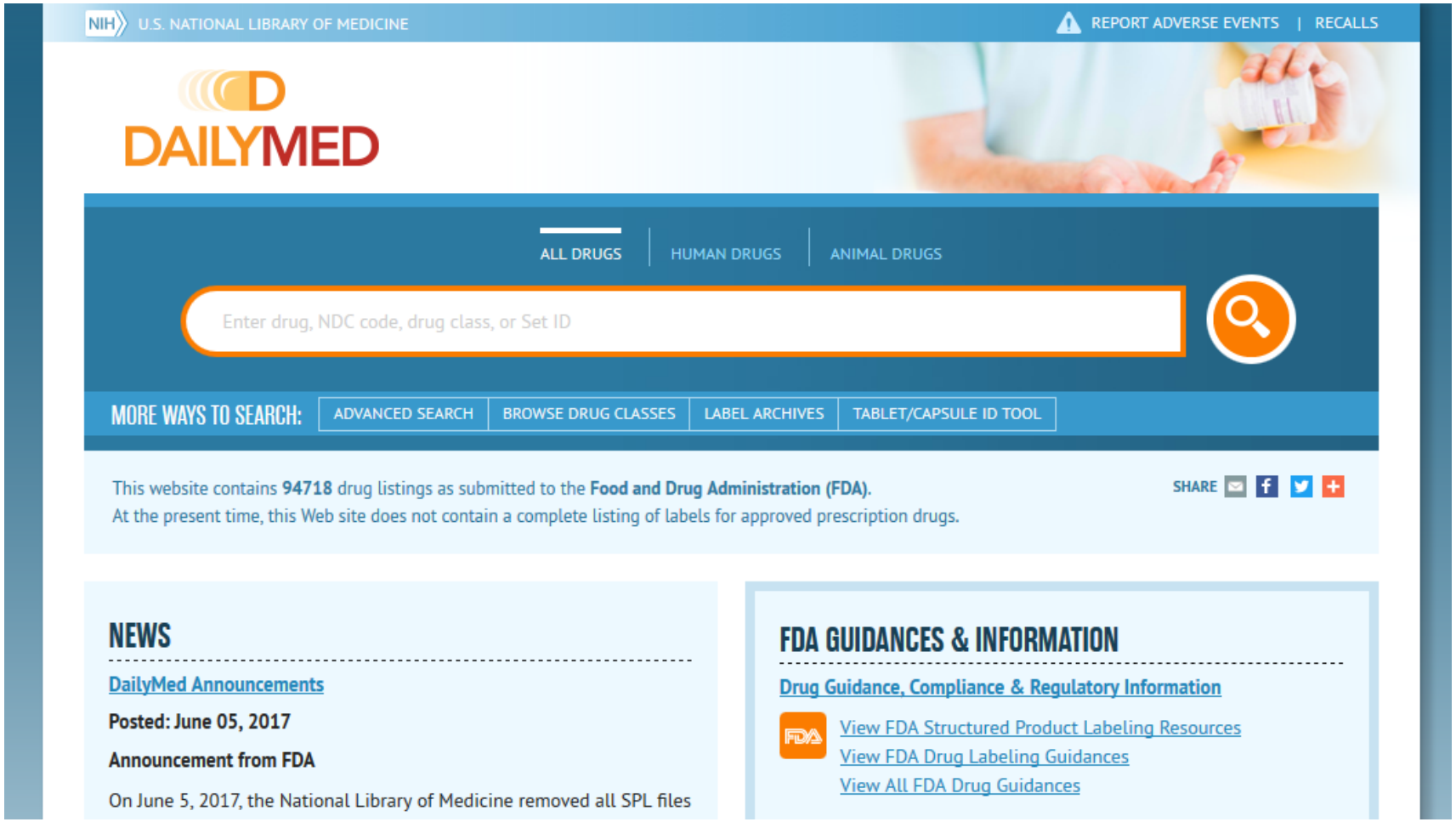
3. Helps integrate REMS into the care process.

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

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

Drug Name, NDA number, dosage form

Approval Date

REMS Elements

Why SPL?

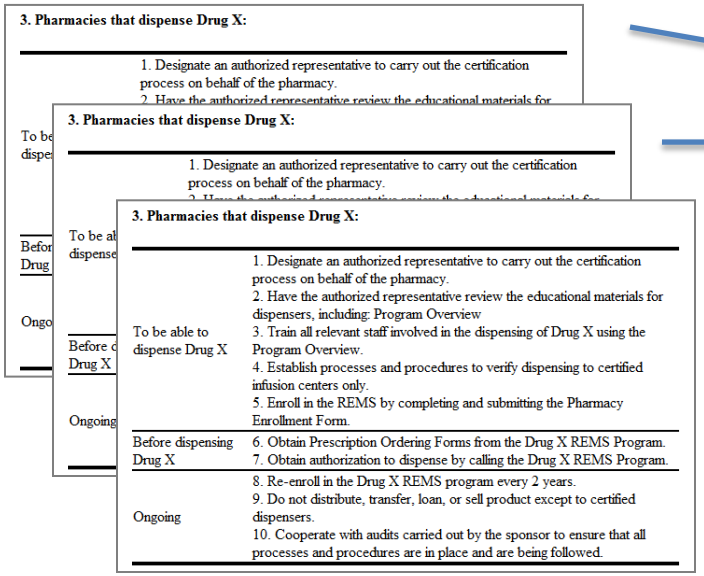
1. Makes REMS information easier to understand.

2. Makes REMS information more accessible.

3. **Helps integrate REMS into the care process.**

REMS Summaries are transformed into standardized data elements

REMS Summaries



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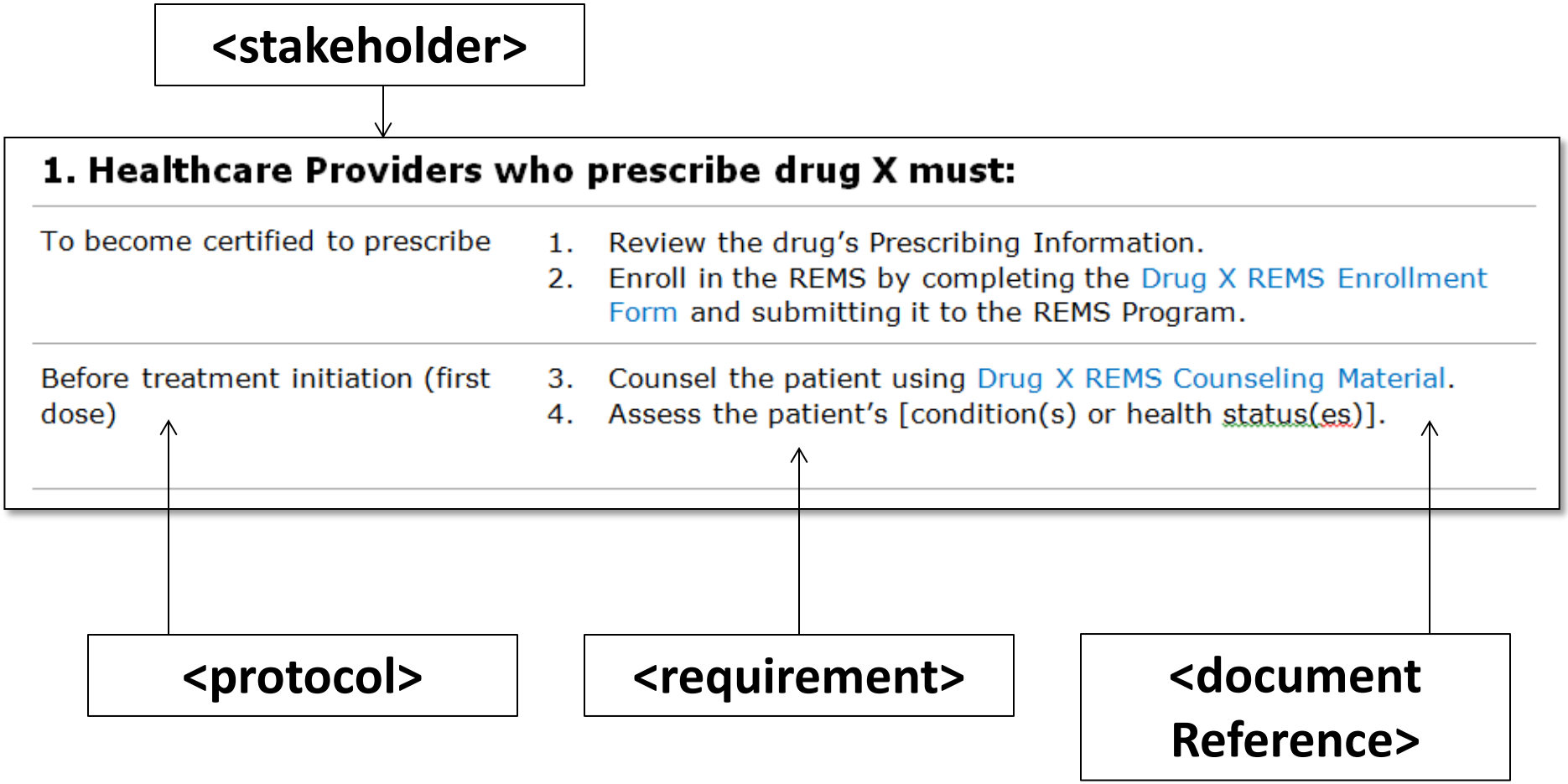
Standardized Data Elements

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

REMS Summary



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

```
<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

What:
- Counsel patient

Who:
- Prescriber

With What:
- documentReference

Codified REMS SPL information can be displayed in many different ways

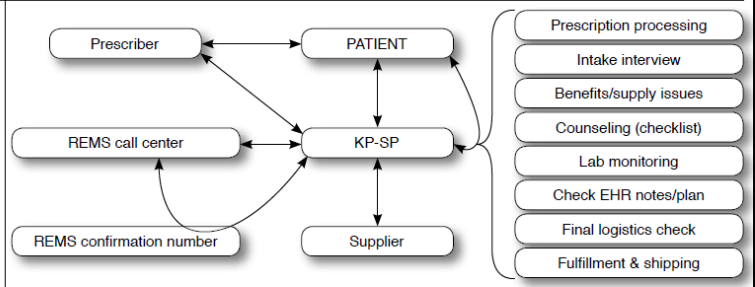
Before/During/After	Activity	Stakeholder	Requirement	Document
before	all activity	dispenser	designate authorized representative	
before	all activity	dispenser	Have representative review educational materials	Program Overview
before	all activity	dispenser	train staff	Program Overview
before	all activity	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	

Use of REMS SPL in the Healthcare System

TABLE 2 Standard Operating Procedures (SOPs)[a]

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	REMS Schematic (simplified example; actual schematic is more complex)
• Medication guide • Communication plan participation • Elements to ensure safe use • Implementation system • Assessment-possible participation	

SP Processes Step-By-Step [Queue-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)

[a]*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

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.

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