U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategies (REMS)

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

Agenda

1. Overview of REMS
   a) Purpose
   b) Legal authority
   c) Tools they employ
2. REMS Assessments and Modifications
3. REMS Requirements for Generics
   a) The single, shared system requirement
   b) Waivers of the single, shared system requirement

What is a REMS?

- **R**isk **E**valuation and **M**itigation **S**trategy
- Authority given by the FDA Amendments Act (FDAAA) in 2007 (Section 505-1 of the FD&C Act)
- A required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks.

Examples of the Types of Risk REMS Requirements Aim to Mitigate

Risk Example	Possible REMS Action
Serious infection	Patient education on initial warning signs prior to prescribing
Severe allergic reaction	Healthcare professional must be certified prior to administer the product
Liver damage	Liver function monitoring while patient is taking the drug
Severe birth defects	Negative pregnancy test prior to dispensing each prescription

When FDA Can Require a REMS

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

REMS: Key Points

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

Possible Components of a REMS

A REMS can include one or more of the following:

- Medication Guide (MG) or Patient Package Insert
- Communication Plan (CP) for Healthcare Providers
- Elements to Assure Safe Use (ETASU)
- Implementation System

Medication Guide

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

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

TRADENAME is:

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

Important information about TRADENAME:

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

Do not take TRADENAME if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

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

When taking TRADENAME:

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

While taking TRADENAME DO NOT:

- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with TRADENAME may cause you to overdose and die.

The possible side effects of TRADENAME:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: *[Insert name and address]* and/or Distributed by: *[Insert name and address]*, www.TRADENAME.com or call1-800-XXX-XXXX

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: month/year

[Click here to see the PDF template online]

Examples of REMS with Med Guide

- Xarelto (rivaroxaban)
  - MG, CP, timetable
    - Goal: To inform nonvalvular atrial fibrillation patients that XARELTO should not be stopped without first informing their healthcare professional so as to minimize the risks of post-discontinuation thrombotic events.
- AndroGel (testosterone gel)
  - MG and timetable
    - Goal: To inform patients about the serious risks associated with the use of AndroGel

Communication Plan

- FDA-approved materials used to aid sponsor's implementation of REMS and/or inform healthcare providers about risks
  - Cannot be directed to patients
- Communication plan may include:
  - "Dear Healthcare Professional" letters
  - Dissemination of information to HCPs through professional societies
  - Information about the REMS to encourage implementation

Example of Communication Plan

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

Elements to Assure Safe Use (ETASU)

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

Elements to Assure Safe Use (ETASU)

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

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

Example of REMS with ETASU

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

Example of REMS with ETASU

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

Implementation Systems

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

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

Timetable for Submission of Assessments

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

REMS Assessments

Must include:

With respect to each REMS goal, an assessment of the extent to which the REMS is meeting the goal or whether one or more goals/elements should be modified

Information Provided in Assessments: Examples

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

REMS Modification

- Applicant may submit REMS modification proposing addition, modification, or removal of any goal or element
  - Must include adequate rationale for proposal
- FDA must review/act on REMS mods within timeframes specified in Guidance

  (Risk Evaluation and Mitigation Strategies: Modifications and Revisions, April 2015)

REMS Modification

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

REMS requirements for generics (ANDA)

- Where innovator product is subject to REMS, ANDA referencing that product is subject to:
  - Med Guide
  - ETASU
    - ANDA must use a ***single, shared system*** with the innovator for any ETASU (unless FDA waives this requirement, in which case ANDA can use different, but comparable system)

Single Shared System REMS

- NDA and all ANDAs
- Single REMS document, REMS materials (except MGs), and supporting documents applicable to all drugs
- Shared database and infrastructure

Benefits of a single shared system

- Reduces burden for different stakeholders
  - single portal to access materials and other documentation and information about the program
  - prescribers, pharmacies, and healthcare settings complete certification and other administrative requirements once rather than for each individual drug
- Potential for cost sharing among all sponsors

SSS Development Process

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

SSS Development Process

1. The Office of Generic Drugs (OGD) notifies each ANDA sponsor of the requirement for a SSS by sending a REMS notification letter.
   - The REMS notification letter (1) notifies the ANDA sponsor of the requirement of a SSS, and (2) directs the ANDA sponsor to contact the sponsor of the reference listed drug.

SSS REMS Development Process (Cont'd)

2. ANDA holders make initial contact with RLD holder and initiate discussions about a SSS REMS
3. FDA hosts a "kick-off" meeting to convey expectations and facilitate planning to move SSS REMS development forward

SSS REMS Development Process (Cont'd)

4. Companies may form an "industry working group" (IWG) to develop a proposal for the shared REMS
   - FDA instructs the IWG sponsors to identify a single point of contact to represent the IWG, and emphasizes the importance of first working out the cost and governance structures
   - IWG provides bi-weekly updates to the Agency
5. The Agency forms a REMS review team including staff from a number of Offices within the Center
   - FDA communicates expected timeframes for milestones
   - FDA schedules periodic teleconferences with the IWG

SSS REMS Development Process (Cont'd)

6. When a company indicates to the Agency that another company (brand or generic) in the IWG is not receptive or responsive to efforts to develop a SSS REMS, the Agency may serve as facilitator to aid in reaching resolution.
7. Once developed, the SSS REMS proposal is submitted by the innovator and generic companies to the Agency for review.
   - FDA instructs the IWG how to submit the REMS proposal.

Issues to be Addressed in Negotiations

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

FDA Perspective on Waiver

- Shared system REMS fulfill Congressional intent to reduce end-user burden and foster ease of access to generic products with REMS.
- The waiver provision provides an alternative path for approval of generic drugs if a single shared system is not feasible.

Waiver of the SSS Requirement

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

Criteria for Waiver

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

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

Criteria for Waiver

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

Separate REMS for ANDA(s)

FDA may waive the requirement for a SSS and permit the ANDA to use a "**different, <u>comparable</u>** aspect" of the ETASU

(505-1(i)).

Separate REMS for ANDA(s)

- Same goals
- Same ETASU
  - Must achieve same level of safety
  - How the elements are operationalized may differ
  - Applicants should explain and justify any differences in operations

Separate REMS for ANDA(s)

Things to consider in developing a separate REMS program:

- Will the operational differences shift burden to other stakeholders?
- Will the operational differences cause confusion for stakeholders?
- Will the operations allow for other ANDAs to join the program?

Waiver Process

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

A Complete REMS Submission

- REMS
- REMS Supporting Document
- Appended materials

Proposed REMS

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

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

REMS Supporting Document

Describes how the program is being implemented

- Whether the element or tools used are compatible with the established distribution, procurement and dispensing systems
- A description of the effectiveness of the proposed program
- Includes metrics that will be used to determine or identify problems with the program and if the goals are being met
- Criteria, methodology or polices that address your management or implementation

Conclusion

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

Information For Industry

Click for:

- REMS Provision in FD&C Act
- FDA REMS Website
- FDA Guidance Documents
- FDA Webinar: REMS Basics
- PDF of the slides for today's sessions

- If we did not get to you question, you can always email to us at:

CDERSBIA@fda.hhs.gov

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

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U.S. FOOD & DRUG ADMINISTRATION

REMS in Structured Product Labeling Format: An Introduction

Adam Kroetsch

FDA | CDER

January 26, 2017

What is SPL?

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

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

Proposal to capture REMS in SPL format was identified by stakeholders (in particular, the National Council for Prescription Drug Programs) and was adopted in 2014 as a “priority project” towards REMS Standardization.

What is SPL not?

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

- For example, prescribers cannot use SPL to enroll in a REMS, prescribe drugs, or monitor patients.
- A related effort, the REMS Platform Standards Initiative, is designed to develop standards to exchange this type of information.

REMS SPL starts with the official "REMS Document"

REMS Document

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

NDA 204819

Adempas® (riociguat tablets)

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

Risk Evaluation and Mitigation Strategy (REMS)

I. GOALS

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

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

II. REMS ELEMENTS

A. Medication Guide

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

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

B. Elements to Assure Safe Use

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

Appended Material

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

Page 1 of 1

Reference ID: 3525688

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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                        <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

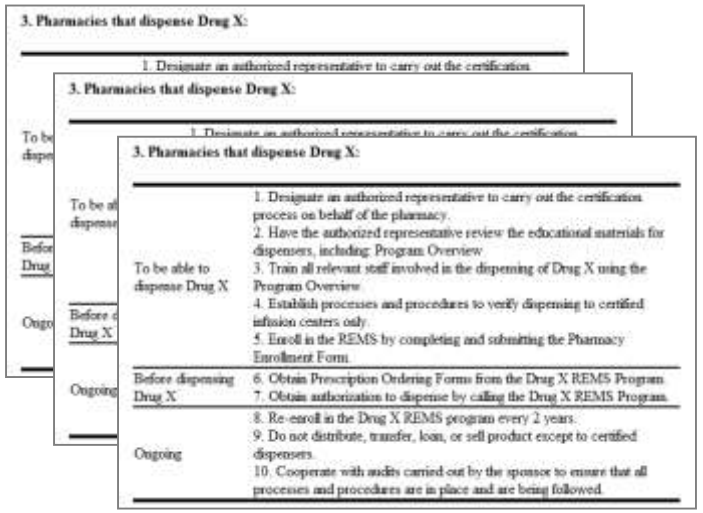
REMS Document Text

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



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?

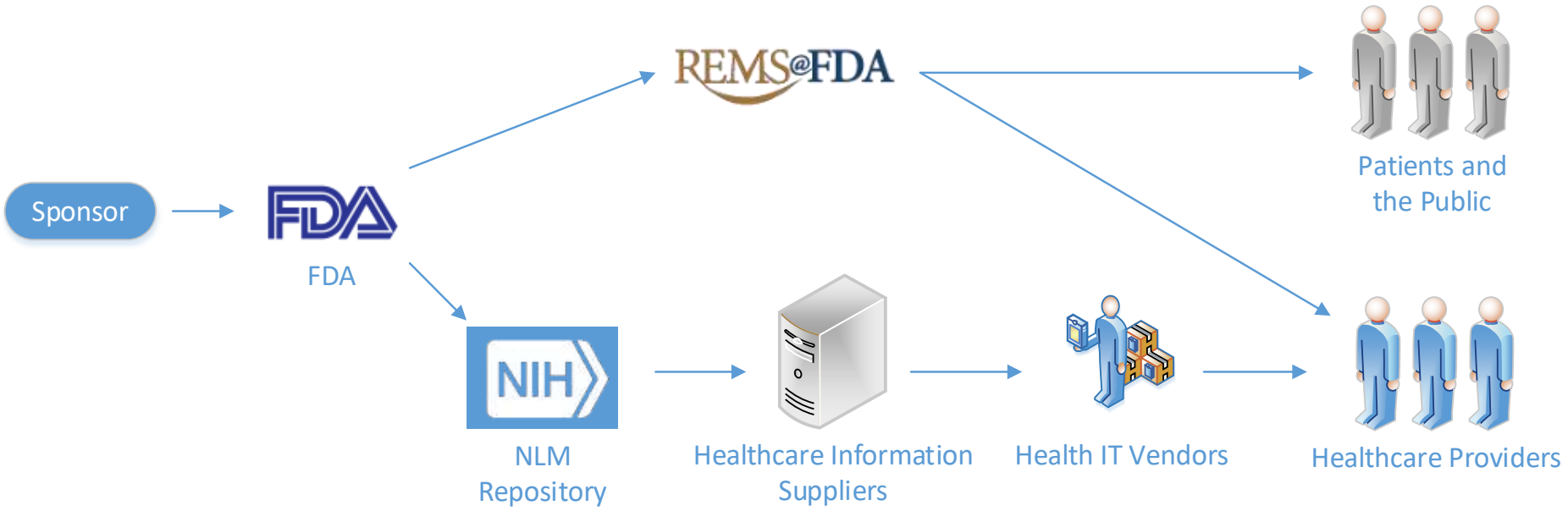
1. Makes REMS information easier to understand.

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

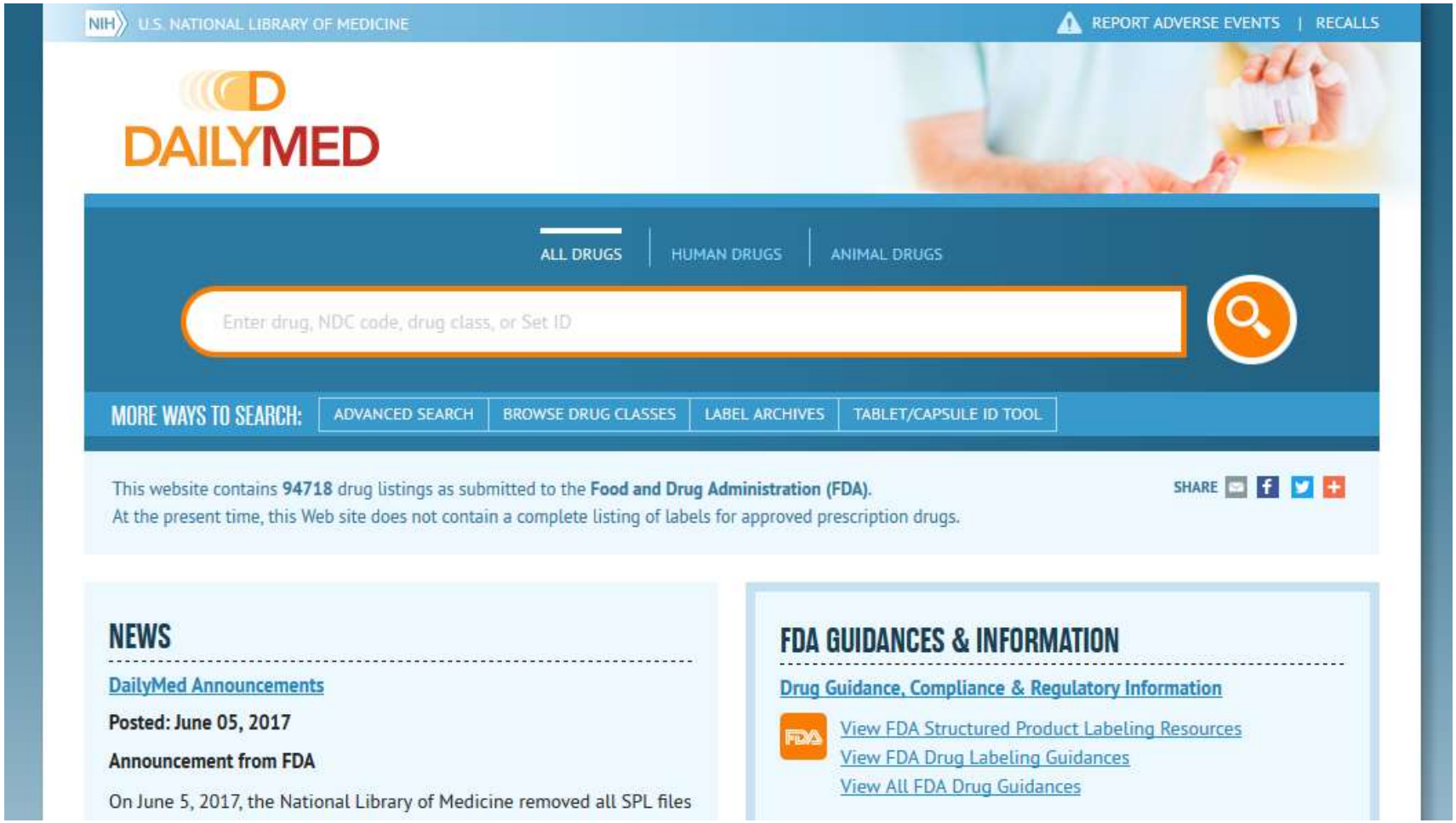
3. Helps integrate REMS into the care process.

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?

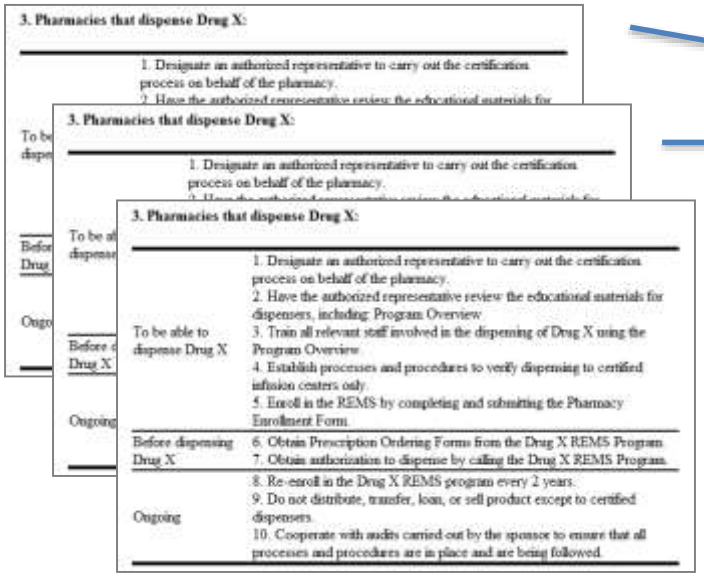
1. Makes REMS information easier to understand.

2. Makes REMS information more accessible.

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

REMS Summaries are transformed into standardized data elements

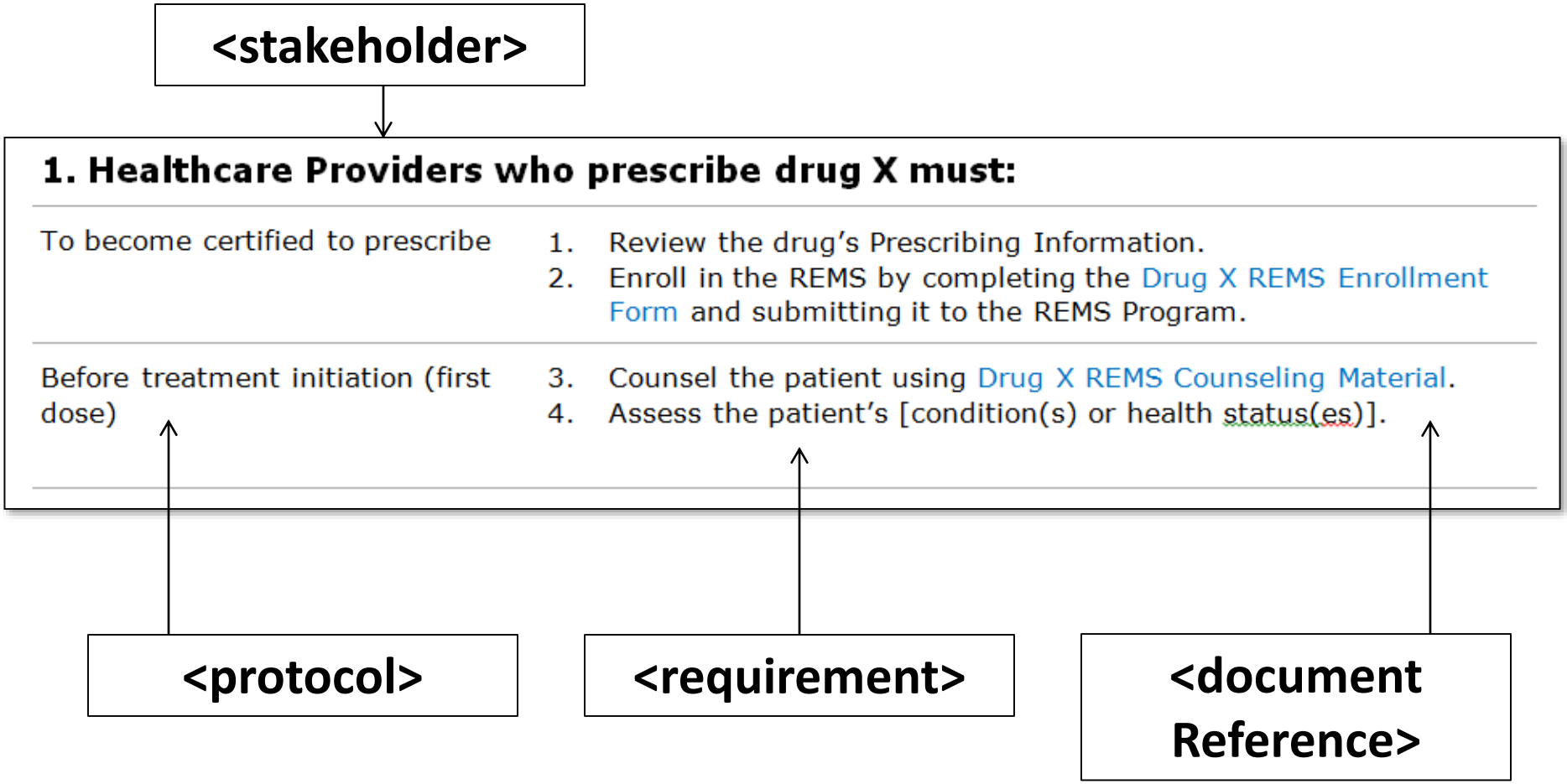
REMS Summaries



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

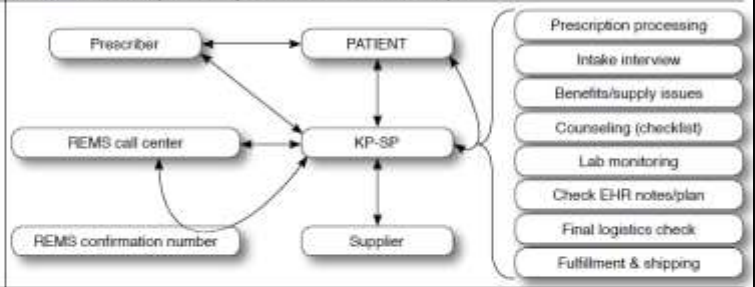
Before/During/After	Activity	Stakeholder	Requirement	Document
before	all activity	dispenser	designate authorized representative	
before	all activity	dispenser	Have representative review educational materials	Program Overview
before	all activity	dispenser	train staff	Program Overview
before	all activity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

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)

**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.

Click Here for Evaluation and Certificate

Learn about other resources from CDER Small Business & Industry Assistance:
Visit Our Website!