

# **Considerations for REMS Surveys and Assessments: Planning and Reporting**

## **CDER SBIA Pharmacovigilance and Risk Management Conference**

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# Objectives



- Understand the requirements for REMS assessments
- Recognize the importance of REMS assessment planning during REMS development
- Describe the components for consideration when developing REMS knowledge survey methodologies
- Describe best practices for conducting REMS assessments and knowledge surveys for REMS assessments

# What is a REMS?

- Risk Evaluation and Mitigation Strategy
- A risk management plan that uses risk minimization strategies beyond professional labeling.
- Designed to achieve specific goals to mitigate risks associated with use of a drug.
- Required to ensure that the benefits of the drug outweigh the risks.



# Components of a REMS

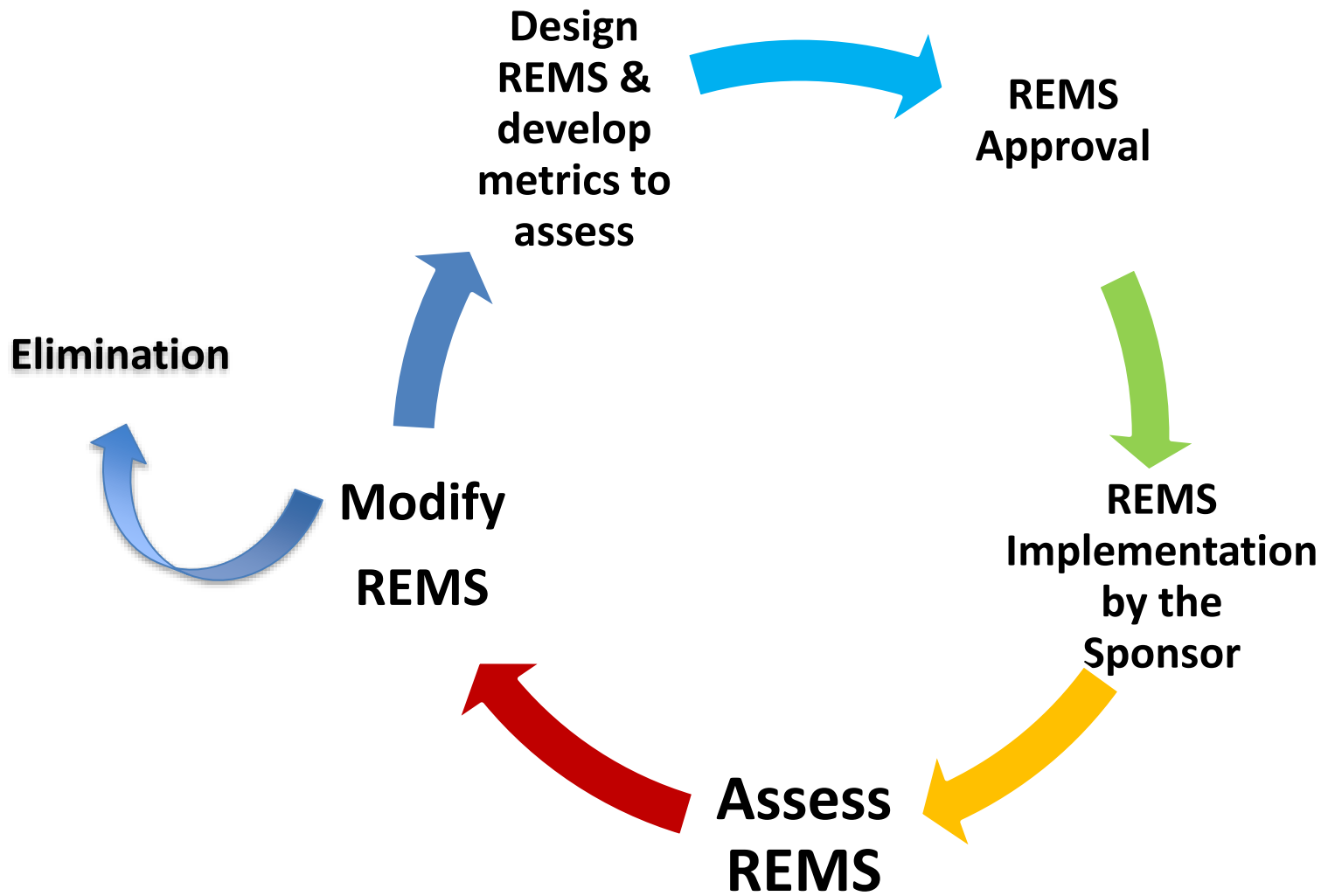
- A REMS can include
  - Medication Guide or PPI
  - Communication Plan for Healthcare Providers (HCPs)
  - Certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose
  - Elements to Assure Safe Use (ETASU)
    - May include restricted distribution
  - Implementation System
- Must include a timetable for submission of assessments of the REMS\*

*\*Note: This requirement applies to NDAs and BLAs only. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS*

# Elements to Assure Safe Use

- ETASUs are medical interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.
- Depending on the risk, a REMS may require one or more of the following:
  - Prescribers have specific training/experience or special certifications
  - Pharmacists or other dispensers be specially certified
  - Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals)
  - Drug be dispensed with evidence of safe-use conditions such as laboratory test results
  - Each patient using the drug be subject to monitoring
  - Each patient using the drug be enrolled in a registry

# REMS are a continuous process



# **REMS ASSESSMENT REQUIREMENTS**

# Requirements - Frequency

The Statute requires the REMS includes:

A timetable for submission of assessments for NDA and BLA assessment submissions

- 18 months, 3 years, and in the 7<sup>th</sup> year after the strategy is initially approved
- At a frequency specified in the strategy; can be increased or reduced in frequency and eliminated under certain circumstances

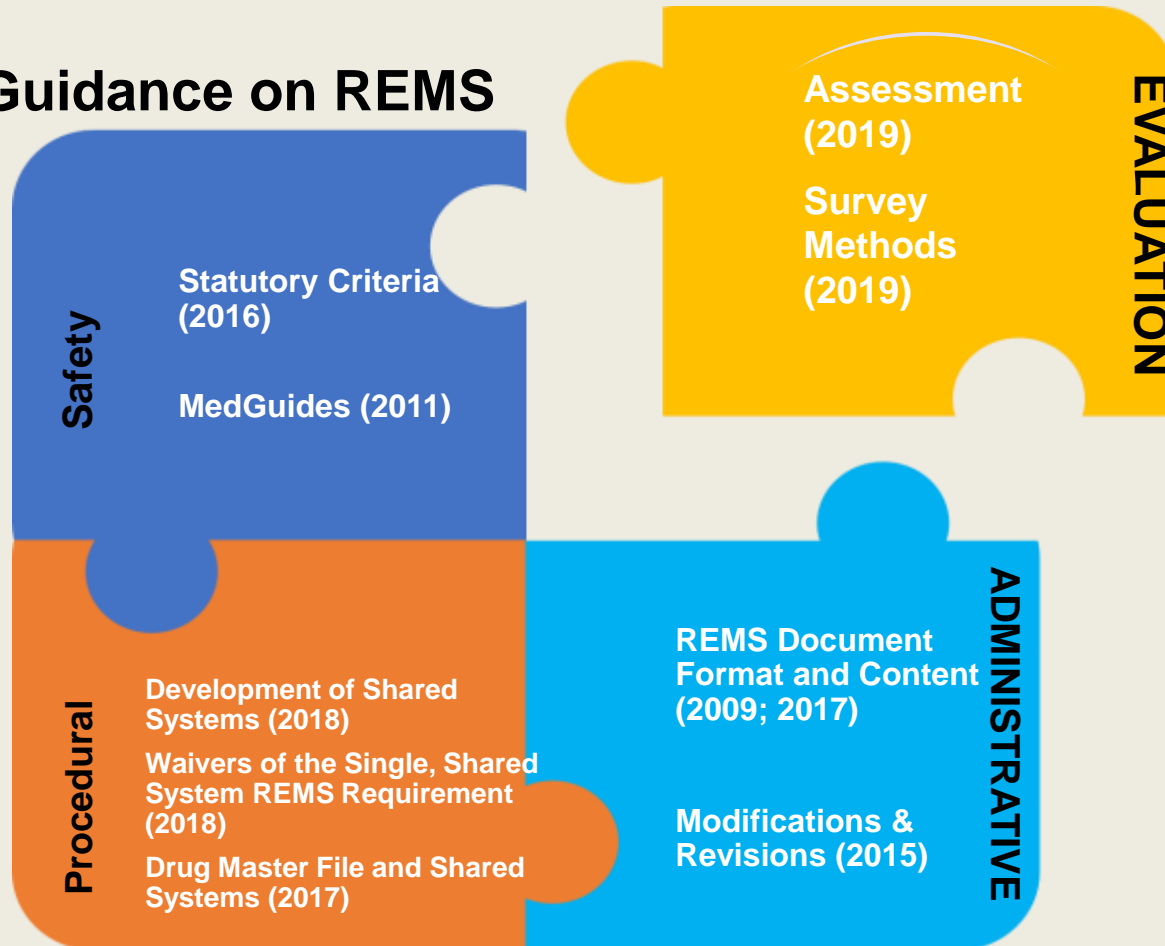


## The Statute states:

- *The assessment shall include, with respect to each goal included in the strategy, **an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more goals or elements should be modified***

# FDA has issued two guidances on REMS Assessments

## FDA Guidance on REMS





# **REMS Assessment: Planning and Reporting Guidance for Industry**

Draft guidance published January 2019

<https://www.fda.gov/media/119790/download>

- Prescription Drug User Fee Act (PDUFA) V Commitment
  - *FDA will issue guidance on methodologies for assessing REMS. This guidance should specifically address methodologies for determining whether a specific REMS **with elements to assure safe use (ETASU)** is: (i) commensurate with the specific serious risk listed in the labeling of the drug and (ii) considering the observed risk, not unduly burdensome on patient access to the drug.*

# REMS Assessment: Planning and Reporting

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# Purpose of this guidance

- Describes how to develop a REMS Assessment Plan, specifically, how the REMS program goals, objectives and REMS design may impact the selection of metrics and data sources, which will be used to assess whether the program is meeting its risk mitigation goals.
- Discusses considerations for assessing the impact of REMS on patient access to the drug and its burden to the healthcare delivery system.
- Provides recommendations on a standardized approach for reporting REMS assessment findings to FDA using the REMS Assessment Report.

# Key messages-

## REMS Assessment Overview

- Assessment plan development should begin with clear goals and objectives
  - Goal and objectives drive REMS requirements, implementation, materials
- REMS design considerations
  - Characteristics of the risk
  - Evidence that the proposed strategy is effective
  - Identification of stakeholders
  - Feasibility of implementing the strategy on stakeholders
  - Healthcare system burden and impact on patient access

# REMS Assessment Plan

Assessment plan – outlines how the applicant intends to assess the performance of the REMS in meeting its risk mitigation goals

- Approval letter – publicly available
  - Can be found at [Drugs@FDA](mailto:Drugs@FDA)
  - Categories and metrics
- REMS Supporting Document – not publicly available
  - Description and rationale for each data source
  - Timeline of methodology submissions



# Key messages-

## REMS Assessment Overview

- REMS assessment plan
  - Consider multiple sources, metrics and methodologies
    - Identify challenges and limitations
  - Novel methods encouraged
    - Examples: smart apps; chart review studies

# Key messages-

## Assessment Plan Development



- Assessment plan should include both process indicators and outcome indicators
- Provide the sources of data and methodological approaches
- Specifying thresholds for effectiveness and the rationale for how they were determined
- Assessment categories and metrics

# Current assessment plan categories and data used to assess REMS

- **Outreach/communication**
  - Target populations: Patients, Healthcare Providers, Pharmacies
  - Numbers of communications sent, opened, returned; stakeholder awareness of REMS
- **Implementation and operations**
  - Enrollment of prescribers, pharmacies, drug utilization, compliance (audits)
- **Safe use behavior**
  - Documentation of lab tests, chart review, Patient Status Forms

# Current assessment plan categories and data used to assess REMS



- **Health Outcomes**

- Events the REMS is mitigating (e.g., Pregnancies with root cause analysis; pregnancy outcomes)

- **Knowledge**

- Stakeholder surveys of knowledge of risk, safe use, and REMS requirements
- Post-training knowledge assessments

# Key messages – Burden and Access Evaluation

- Identify potential burdens/barriers to access during REMS development
- Describe how burden/barriers to access have been minimized in REMS design
- Plan for evaluation of burden/barriers to access

# Assessment report format



- Cover page
- Table of contents
- 1. Executive summary
- 2. Introduction
- 3. Background
- 4. REMS assessment plan
- 5. Summary of previous assessments
- 6. Results or summary of findings for each assessment metric
- 7. Discussion: overall assessment of whether the REMS goals and objectives are being met
- 8. Proposed modifications to the REMS or revisions to the REMS Assessment Plan

# **Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance for Industry**

Draft guidance published January 2019

<https://www.fda.gov/media/119789/download>

# Outline of this guidance

- Background
- Endpoints of Interest
- Sampling and Participant Recruitment
- Sample Size
- Survey Conduct
- Questionnaire Development
- Analyzing and Presenting Results
- Next Steps



# Background



- Most REMS include a goal to inform or educate healthcare providers and/or patients about the serious risk associated with and safe use of the drug.
- When there is a goal to inform or educate, the assessment plans usually requires an evaluation of knowledge.
- Applicants most often use surveys to evaluate if the REMS is meeting this type of goal.
- In 2012, FDA held a public workshop on methodologies to assess REMS goals related to knowledge. Input from the workshop and docket comments were incorporated into the guidance.

# Endpoints of Interest

- In a target population, the endpoint is the knowledge rate of a REMS key message.
- Defined knowledge rate as the proportion of respondents who know the key message out of all respondents.
- The methodology should define the REMS key messages and how each endpoint will be calculated from the survey items.

# Endpoints of Interest

- Example of endpoints of interest:
  - Proportion of prescribers who know about the serious risk
  - Proportion of prescribers who know the patient monitoring requirements
- Applicant should pre-specify a performance threshold that if achieved indicates the REMS met the goal
  - Determined on a case by case basis but recommend to be set at 80% or higher
  - Include justification for the pre-specified threshold; informed by public health implication of lack of knowledge

# Sampling and Participant Recruitment

- Variation in selecting a sampling frame based on the REMS requirements
- If the REMS requires patient, prescriber, or pharmacy enrollment, the associated databases should be used as the sampling frame
- If a REMS does not include mandatory databases, possible sampling frames could be lists from chain pharmacies or voluntary registries
- From the selected frame, we recommend using a probability random sample
- Recommend using a multimodal approach to recruit and provide strategies to minimize non-response

# Sample Size

- Number of subjects invited to participate should be larger than the target sample size to account for nonresponse
- Sample size calculations depends on:
  - Sampling design. Examples of probability sampling designs are simple random sample, stratified random sample, and cluster sample
  - Precision. Determined on a case by case basis but recommend it should be set at 5% or less
  - Assumed knowledge rate. Based on a best guess. 50% is conservative, as it yields the largest sample size estimate
  - Target population size

# Survey Conduct



- Provide general eligibility criteria for patient, healthcare provider, and pharmacist participants
  - Criteria can be modified based on the specifics of the REMS
- Applicants should inform the participants that the survey is voluntary and that their answers will not affect their ability to prescribe, dispense, or receive the drug
- REMS education materials should not be provided during the survey.
  - Recommend showing a sample of the material to make it easier for identification

# Questionnaire Development

- Recommend pre-testing of the survey instrument
- The surveys should use a variety of question types
- The questions should be framed based on the information in the PI or REMS materials, not on the respondents experience or opinion.
  - Ex: According to the Prescribing information, Drugs X can cause which of the following serious side effects?
- Include questions to assess knowledge, receipt, and source of REMS materials

# Analyzing and Presenting Results



- Provide a comparison of the characteristics of the respondents to the known characteristics of the target population and discuss reasons for differences
  - If possible, provide a comparison between non-responders and responders
- When the number of completed surveys is higher than the expected number, data from all of the surveys should be included in the analysis
- Consider unanswered survey questions as missing and instead of incorrect.
- Should report the number of respondents who reported each answer choice



# Next Steps

- Currently reviewing and addressing the docket comments
- Considering the addition of information on sampling small populations and techniques/methods to attempt to minimize non-response

# **BEST PRACTICES AND POTENTIAL CHALLENGES**

# Best Practices for REMS Assessment Planning

- Outcomes for a successful REMS should be clearly defined before developing REMS
  - Assessment metrics should map back to the goals and requirements of the REMS
  - Ideally REMS design allows for appropriate data collection to assess certain aspects of the program
- REMS assessments should include a variety of methodologies and data sources
  - Methodologies should be submitted for agency review prior to beginning the evaluation
  - Justification for study type should be provided in the proposed protocols

# Potential challenges

- Establishing thresholds
  - Determining performance thresholds can be difficult but are necessary.
- Determining the effect of the REMS
  - It may be difficult to distinguish the effect of the REMS from other healthcare or public health initiatives.
- No baseline data
  - For a REMS that is established at the time of initial drug approval, there often is no baseline data to use as a comparison

# Potential challenges-cont.



- Available data sources
  - For drugs that are infrequently prescribed some commonly used data sources may not have sufficient data to be able to study the impact of the REMS.
- Small populations
  - Safety-related health outcomes that are the focus of the REMS may occur rarely and thus be challenging to measure and accurately evaluate using available data sources.
- Recruiting and response rates
  - Results may not be generalizable

# Challenge Questions

- Which of the following statements are true?
  - a) REMS assessments are required only for REMS with elements to assure safe use
  - b) All methodologies used in REMS assessments should be submitted for FDA review
  - c) Patients who are enrolled in REMS programs must agree to participate in REMS knowledge surveys
  - d) A and C only
  - e) All of the above

# Challenge Questions



- What is an appropriate knowledge performance threshold for a REMS survey key message?
  - a) 80 percent or higher
  - b) A threshold that is determined on a case-by-case basis that is informed by the public health implications of a lack of knowledge
  - c) Both A and B
  - d) None of the above

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