Division of Risk Management's Role in the Review of Risk Evaluation and Mitigation Strategies (REMS)

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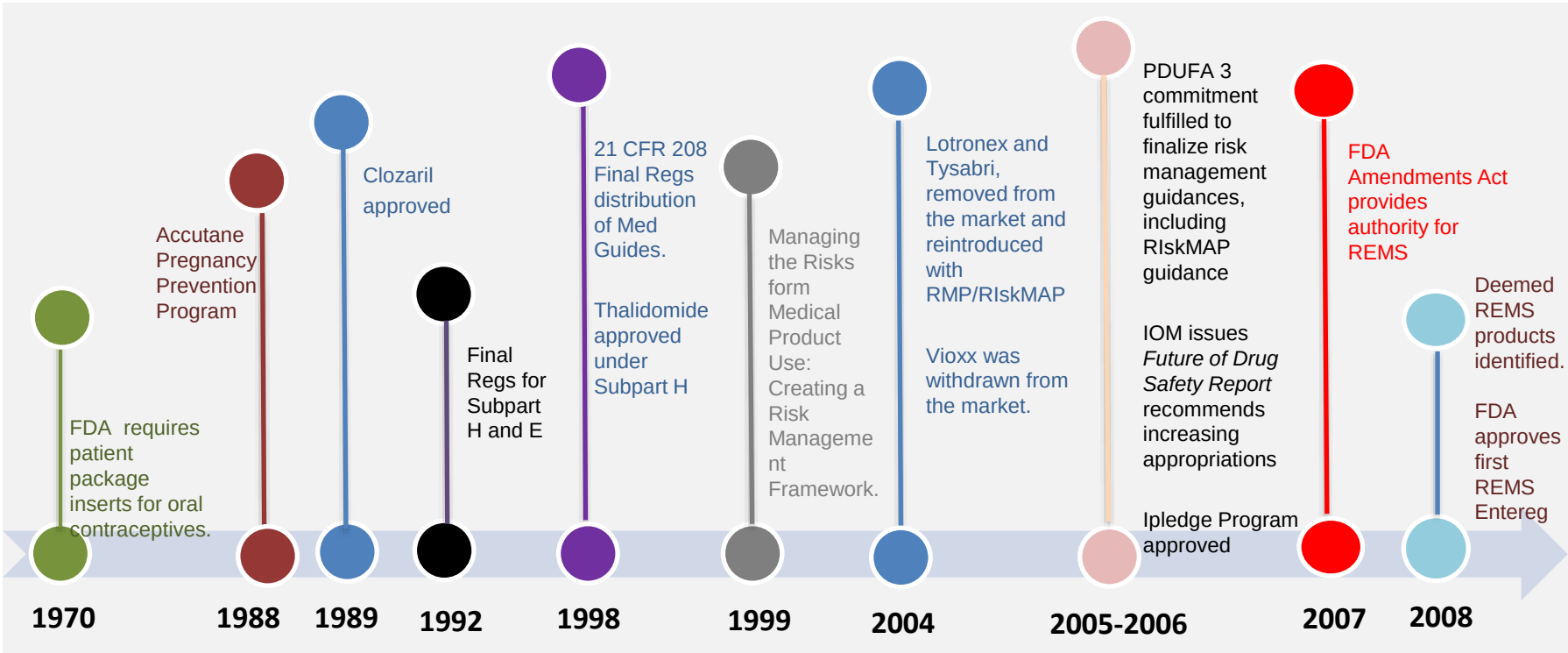
Pharmacovigilance and Risk Management Conference
June 9, 2020

Learning Objectives

- Understand when the Agency can require a REMS
- Describe the types of changes that can be made to REMS
- Identify all the components of a complete REMS submission
- Describe the role of DRM in the life cycle of a REMS

FDA Risk Management Over the Years



Risk Evaluation and Mitigation Strategy (**REMS**)

- A required risk management plan that uses risk mitigation strategies **beyond** FDA-approved professional labeling.
- FDA Amendments Act (FDAAA) of 2007 added Section 505-1 to the Food Drug and Cosmetics Act which authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.

- Applies to NDAs, BLAs, and ANDAs.
- REMS can be required pre- or post-approval

Updates to REMS Authorities

FDA Safety and Innovation Act (FDASIA) July 2012

1st Century Cures Act - Dec 2016

Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act Oct 2018

Appropriations Act of 2020

Statutory factors for determination of a REMS

- Estimated size of the population likely to use the drug
- Seriousness of the disease or condition to be treated
- Expected benefit of the drug
- Duration of treatment with the drug
- Seriousness of any known or potential adverse effects related to the use of drug and background rate of such events in population likely to use the drug
- Whether a drug is a new molecular entity (NME)

Components of a REMS

A REMS can include:

- Medication Guide or Patient Package Inserts (PPI)
- Communication Plan for Healthcare Providers (HCPs)
- Certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose
  - New authority under the SUPPORT Act of October 24, 2018
- Elements to Assure Safe Use (ETASU)
  - May include restricted distribution
- Implementation System
- Timetable for submission of assessments

A REMS can include one or more the following ETASU

- 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

FDA Guidance on REMS

Early Guidances pertaining to Risk Management

Under PDUFA III, FDA agreed to produce guidance for industry on risk management activities for drug and biological products.

Premarketing Risk Assessment (Premarketing Guidance)	**Development and Use of Risk Minimization Action Plan (RiskMAP Guidance)**	**Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)**

Many of the principles that were included in the RiskMAP guidance are embodied in the REMS provisions as implemented by FDA.

Early REMS Guidance

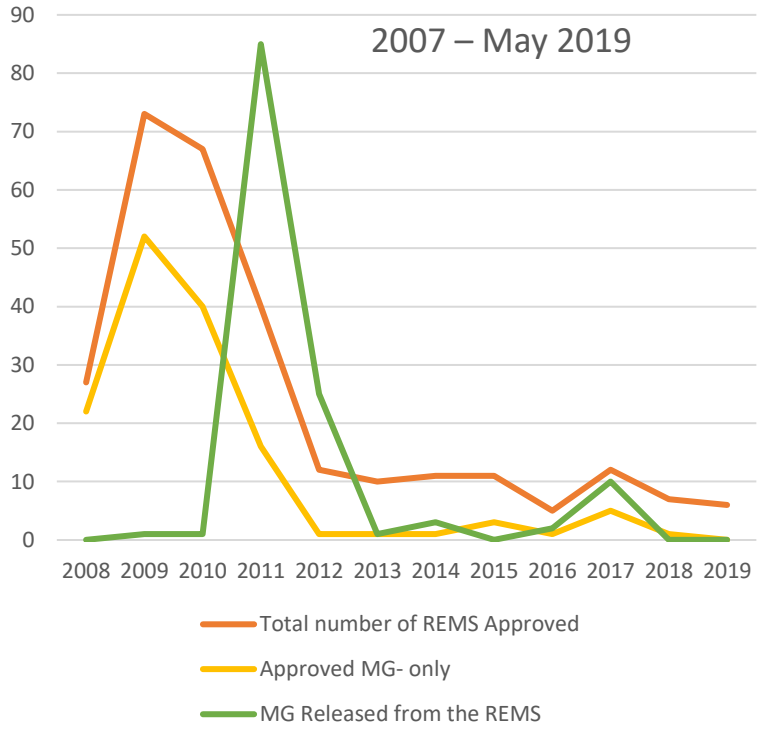
2009 Draft Guidance for Industry: *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications.*

- Provided FDA's thinking at that time on the format and content that industry should use for submissions of proposed REMS
- Described each potential element of a REMS
- Included preliminary information on the content of assessments and proposed modifications of approved REMS
- Eventually replaced by newer guidance

Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)

Early after the REMS authorities were implemented all new Medication Guides were approved with a REMS.

In 2011, FDA reversed that policy by issuing this guidance. The guidance describes when a Med Guide will be required as part of a REMS



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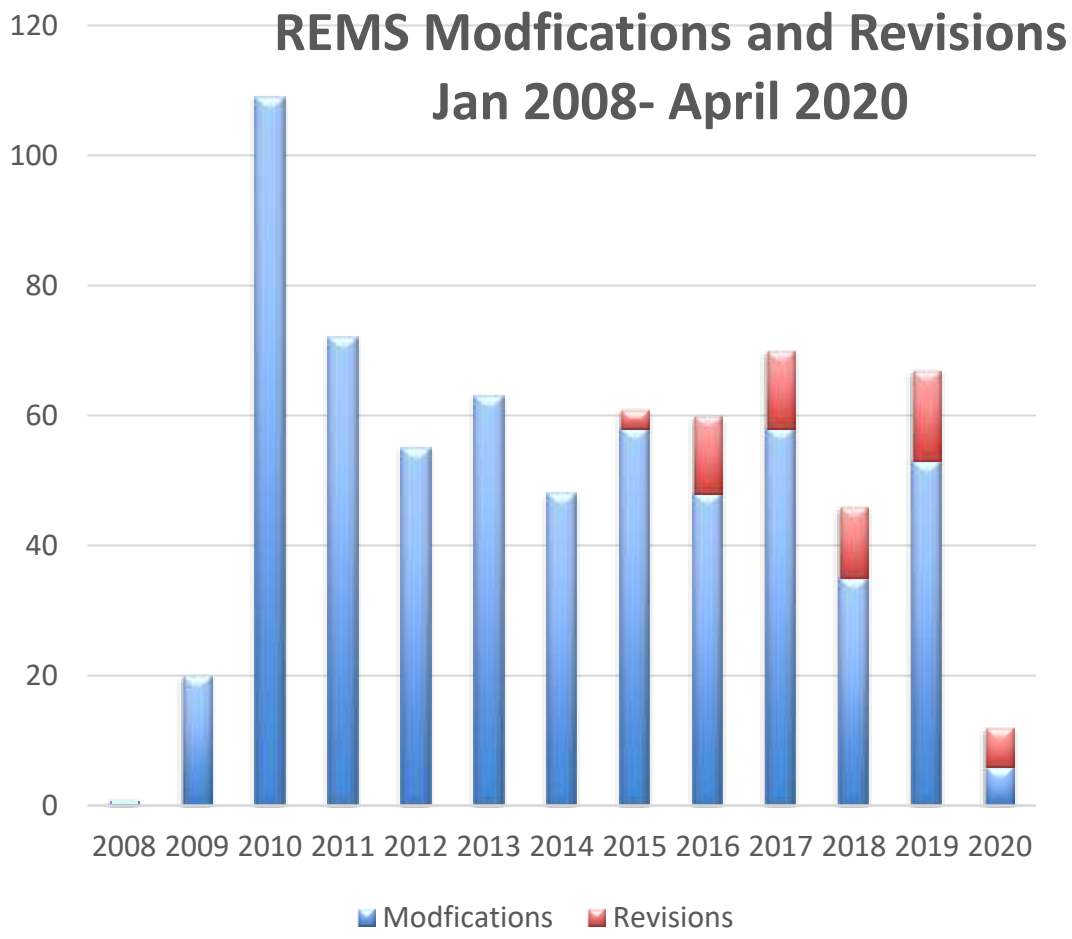
REMS: Modifications and Revisions

The Food and Drug Administration Safety Innovation Act of 2012, or ***FDASIA,*** amended the provisions for modification of REMS that included:

- REMS revisions
- minor REMS modifications
- major REMS modifications
- REMS modifications due to safety labeling change

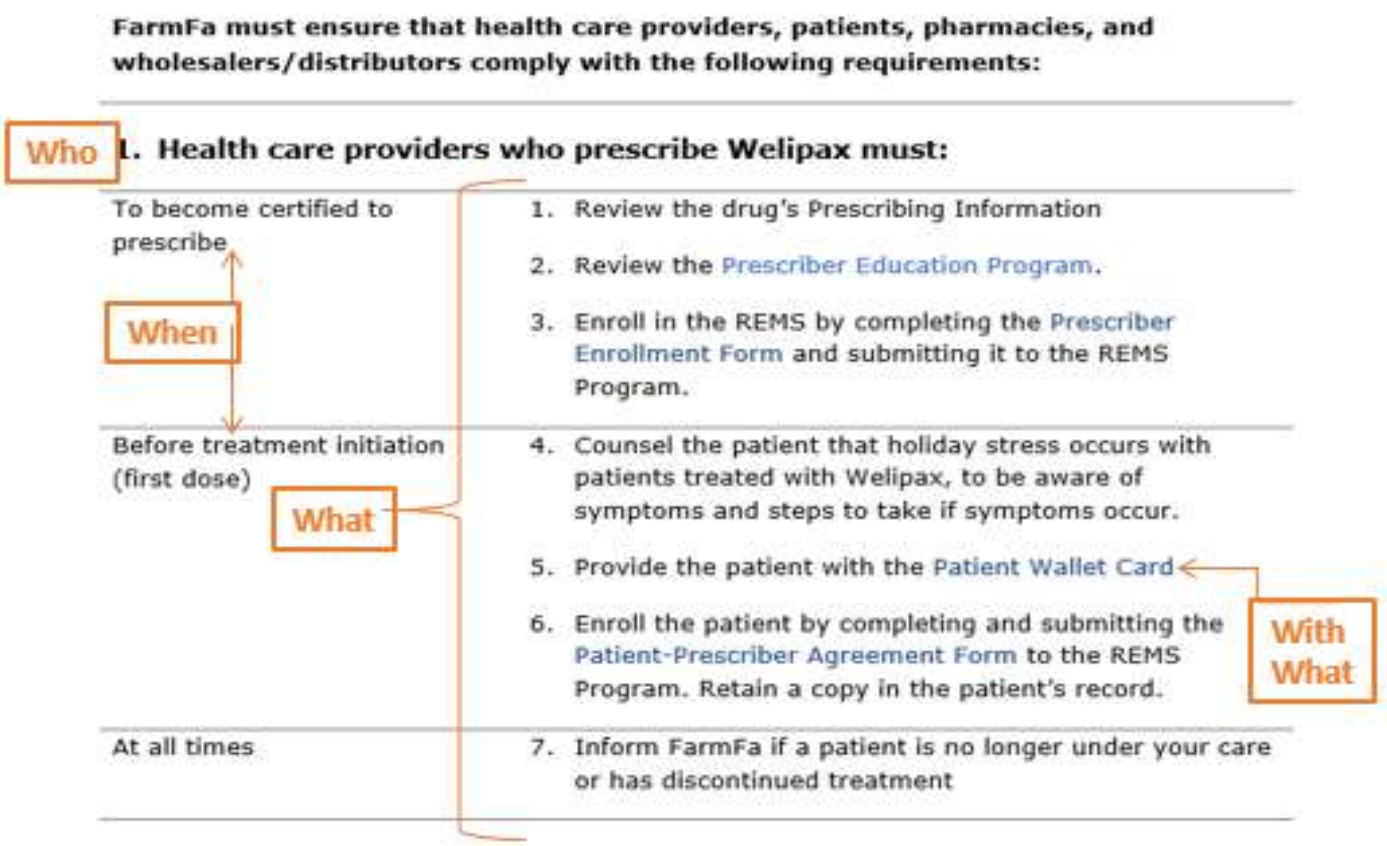
Draft guidance was published in 2015; finalized in 2019



Draft Guidance - Format and Content of a REMS Document

- Published in 2017
- Standardizes concepts
- Provides updated recommendations on the format and content of the REMS document based on feedback from stakeholders
- More clearly communicates what is required of each stakeholder
- Supports submission of a REMS document in Structured Product Labeling (SPL) format
- REMS@FDA website uses a similar format

REMS Document – 2017 Template



FarmFa must ensure that health care providers, patients, pharmacies, and wholesalers/distributors comply with the following requirements:

Who

1. Health care providers who prescribe Welipax must:

When	What
To become certified to prescribe	1. Review the drug's Prescribing Information 2. Review the Prescriber Education Program. 3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.
Before treatment initiation (first dose)	4. Counsel the patient that holiday stress occurs with patients treated with Welipax, to be aware of symptoms and steps to take if symptoms occur. 5. Provide the patient with the Patient Wallet Card 6. Enroll the patient by completing and submitting the Patient-Prescriber Agreement Form to the REMS Program. Retain a copy in the patient's record.
At all times	7. Inform FarmFa if a patient is no longer under your care or has discontinued treatment

With What

Additional REMS Guidance

- 2017 - Draft Guidance -Providing Regulatory Submission in Electronic Format- Content of the REMS Document Using Structured Product Labeling

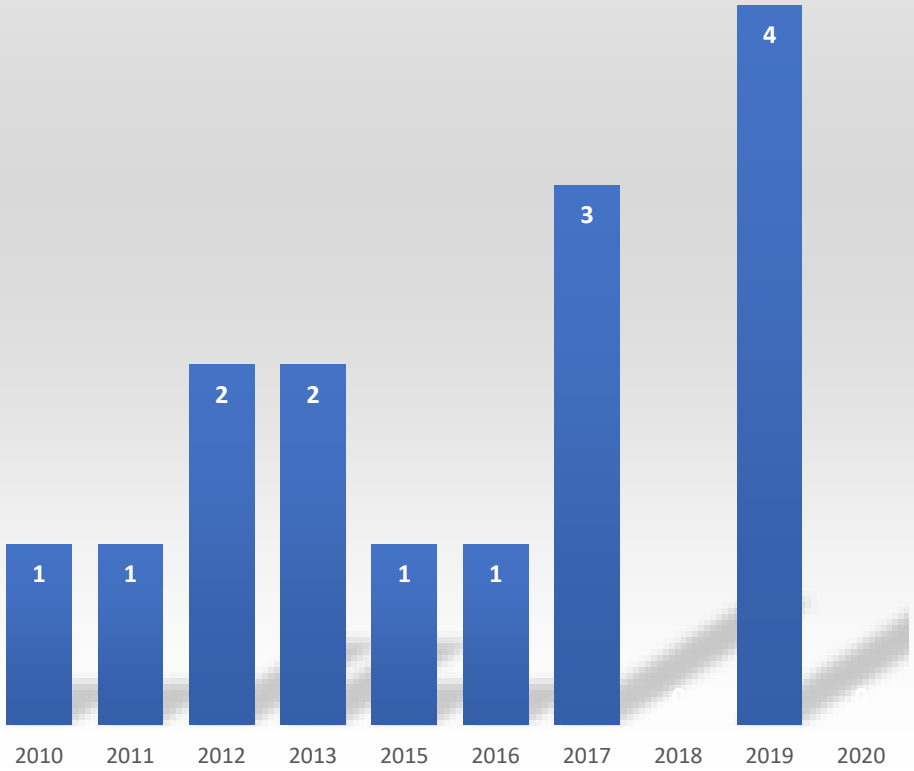
- 2019 FDA's Application of Statutory Factors in Determining When a REMS is Necessary

- 2019 Draft - REMS Assessment: Planning and Reporting

- 2019 Draft- Survey Methodologies to Assess REMS Goals That Relate to Knowledge

Shared System REMS

Oct 2010 - May 2020

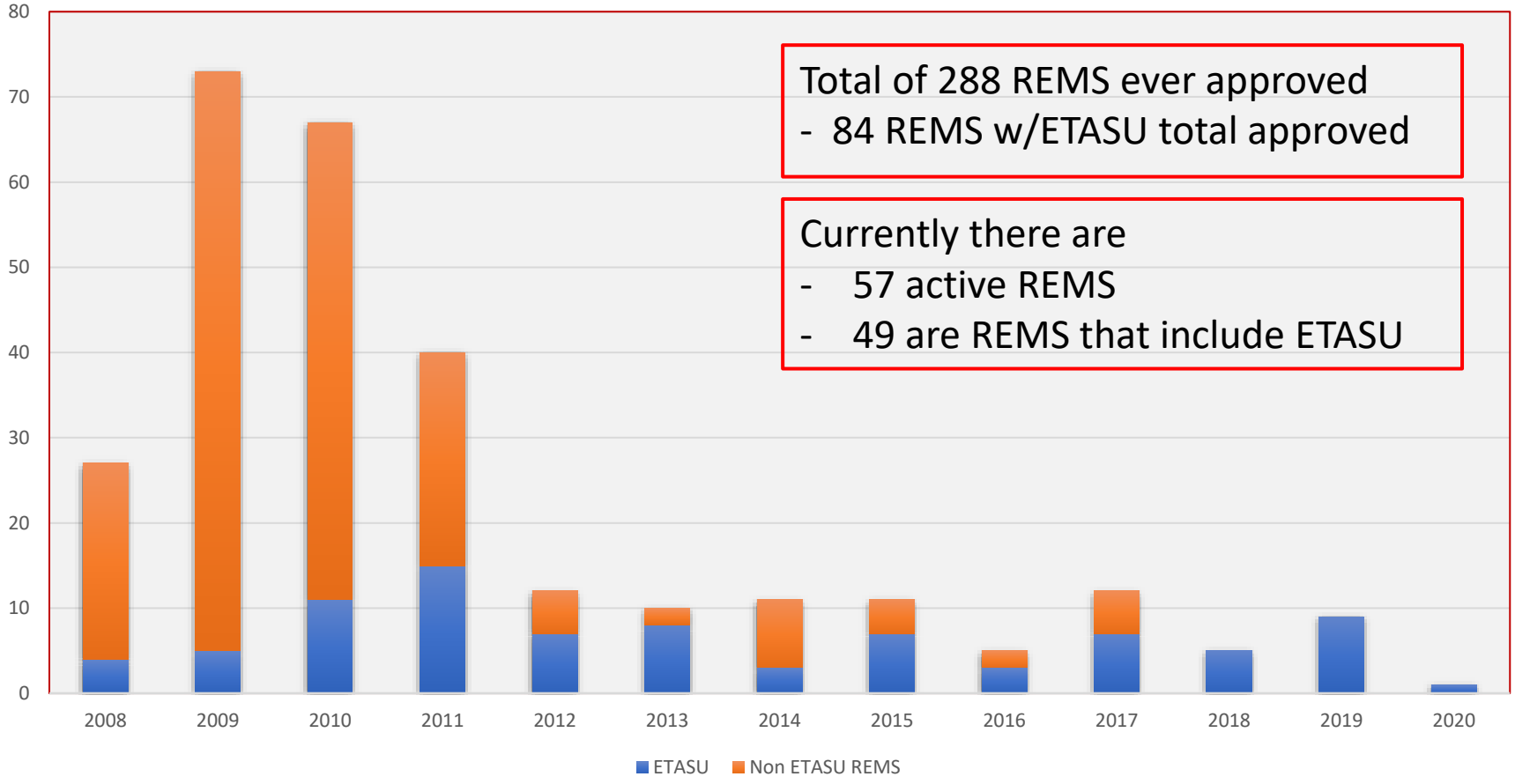


Draft- Development of a Shared System REMS

Draft – Use of the Drug Master File for Shared System REMS Submission

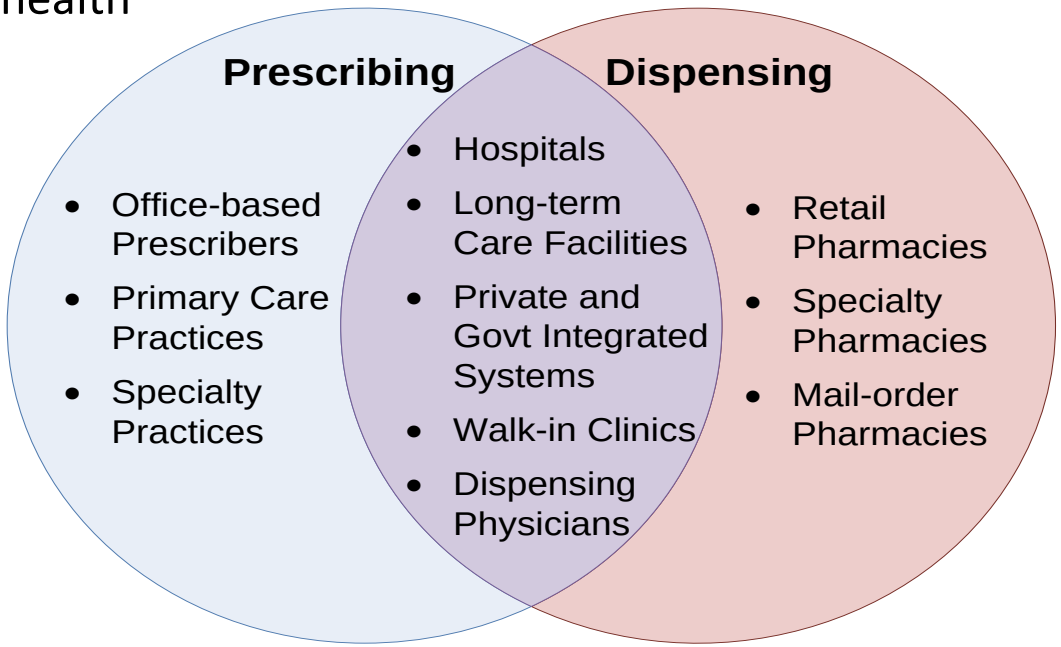
Total REMS Approved

2008- May 2020



Designing and implementing REMS can be challenging

- Significant diversity in the health system
- Healthcare technology is continuously evolving
- REMS authorities may not completely align with how health care is delivered



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Challenge Question #1

The Food and Drug Administration Act (FDAAA):

A. Promotes Opioid Recovery and Treatment for Patients and Communities for 30 days.

B. Details how to make structured REMS information available to patients and healthcare providers.

C. Creates and Restores Equal Access to Equivalent Samples.

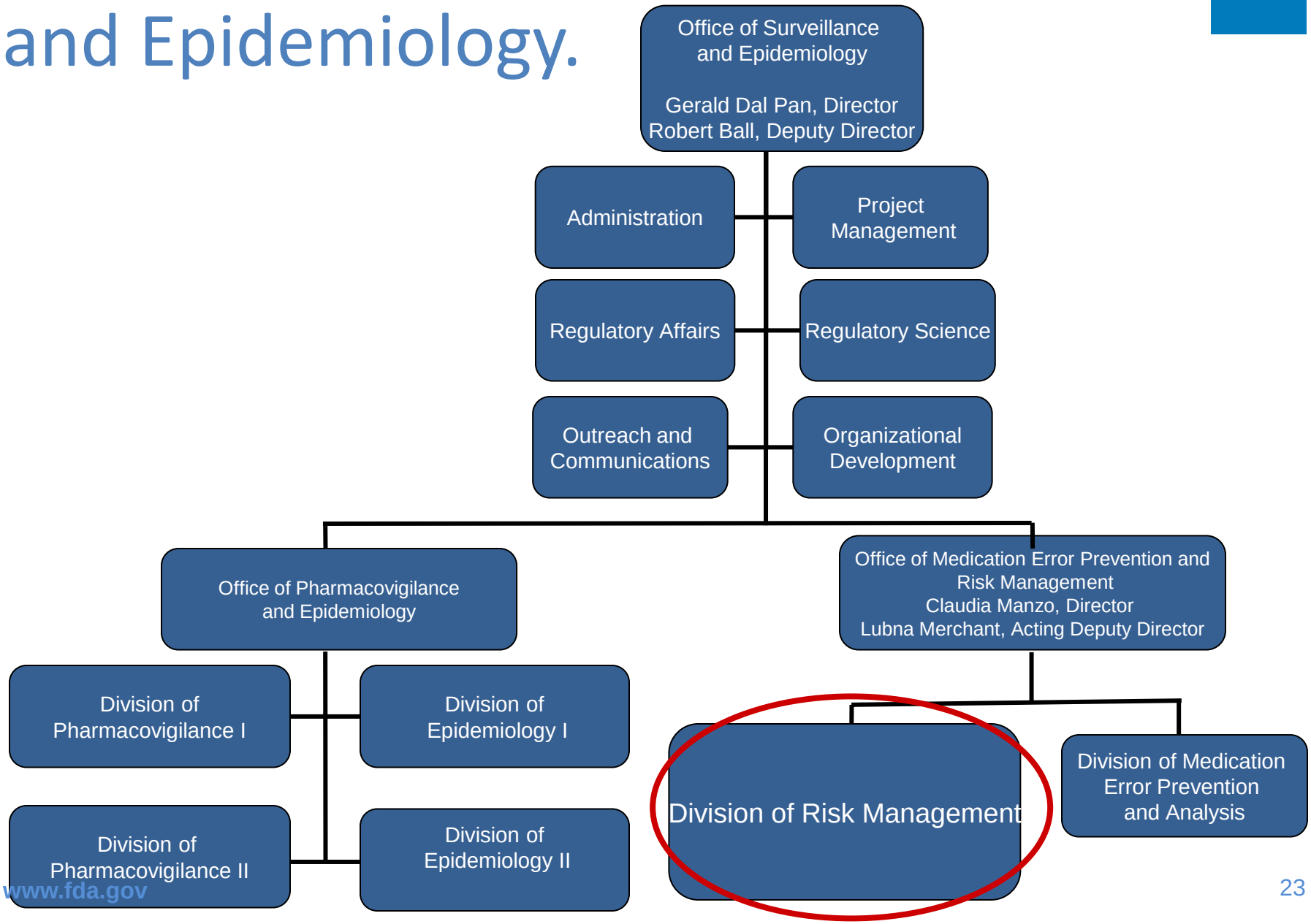
D. Authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure benefits outweigh the risks.

REMS Guidances

- **2011** Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)
- **2017** *Draft* - Format and Content of a REMS Document
- **2017** *Draft* -Use of Drug Master File for Shared System REMS Submission
- **2017** *Draft* – Providing Regulatory Submissions in Electronic Format-Content of the REMS Strategies Document Using Structured Product Labeling
- **2018** *Draft* – Waivers of the Single, Shared System REMS Requirement
- **2018** *Draft* - Development of a Shared System REMS
- **2019** FDA's Application of Statutory Factors in Determining When a REMS is Necessary
- **2019** *Draft* - REMS Assessment: Planning and Reporting
- **2019** *Draft* - Survey Methodologies to Assess REMS Goals That Relate to Knowledge
- **2019** Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Division of Risk Management (DRM)

DRM is in the Office of Surveillance and Epidemiology.



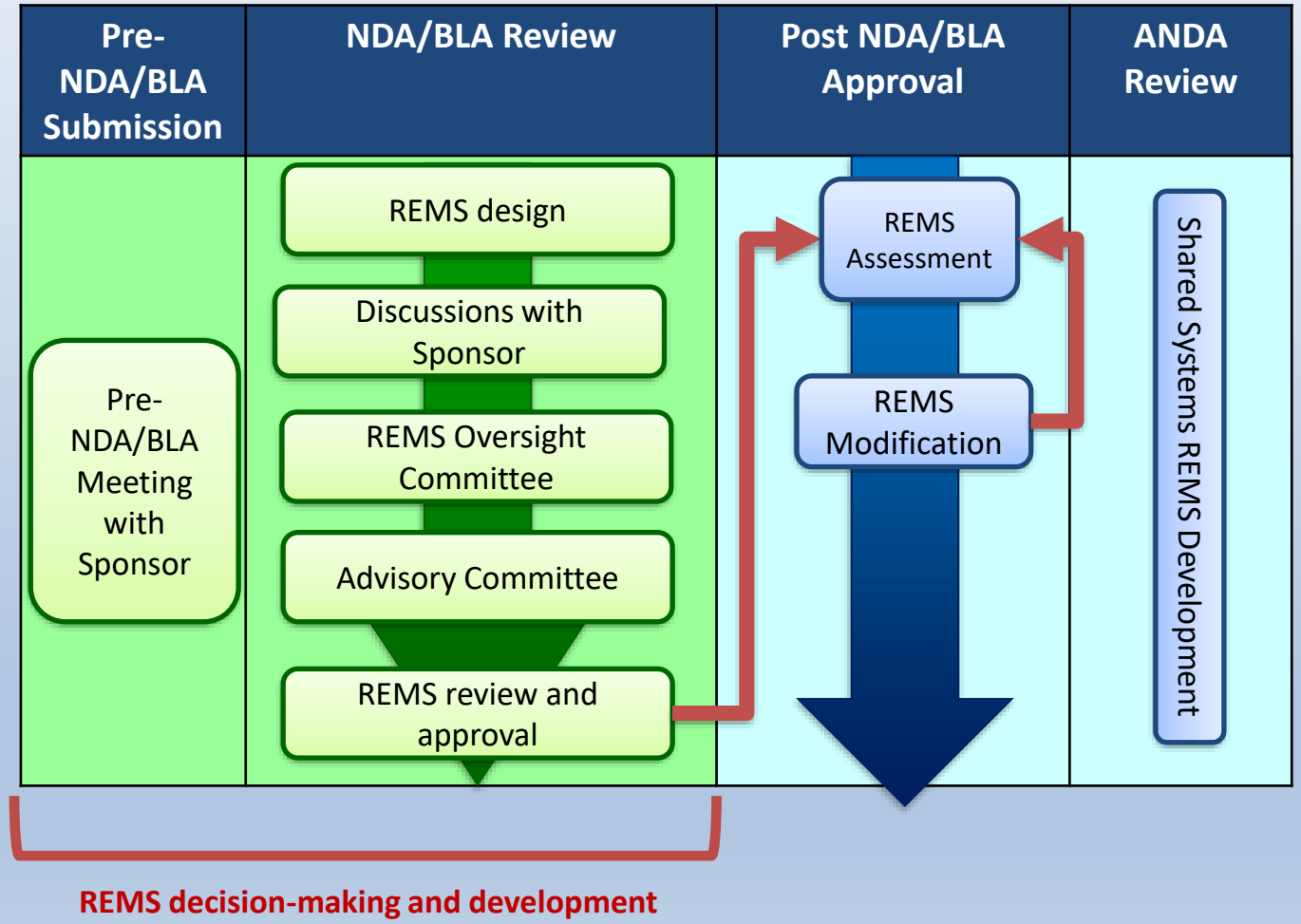
DRM Mission

- To protect public health and promote safe and effective use of drugs by developing and evaluating strategies to minimize serious risks of drugs and effectively communicate drug risks.

DRM is the focal point for Risk Management in CDER

- Serve as the focal point of the CDER REMS Program and for REMS activities in CDER.
- Conduct evaluations of all NMEs, original BLAs, and other applications for new drugs for determination of the need for additional risk mitigation.
- Conducts review of preapproval and postapproval proposed REMS submissions.
- Conducts review of proposed REMS modifications, REMS assessment methodology, and REMS assessment reports.

REMS Lifecycle Review Activities



Pre-Market Review

Risk management discussion often begins at the Pre-NDA/Pre-BLA Meeting.

Held in advance of the planned submission of the application

DRM will address questions related to REMS

DRM reviews submissions for all NMEs and some non-NMEs.

All NME submissions are analyzed by DRM for the need for a REMS.

505(b)2 applications and ANDA applications may also be reviewed by DRM if they reference a drug subject to a REMS, pose a new safety risk, or a part of a class-wide REMS.

A determination regarding the need for a REMS to ensure the benefits outweigh the risks will include consideration of the six FDAAA factors and other criteria

If an application is determined to need a REMS to ensures the benefits outweigh the risks

- Agency will determine the goals of the REMS and alert sponsors to any required elements.
- The Agency will not approve an application or efficacy supplement without an acceptable REMS.

If a REMS is required, the sponsor should submit a complete REMS submission.

A complete REMS submission includes:

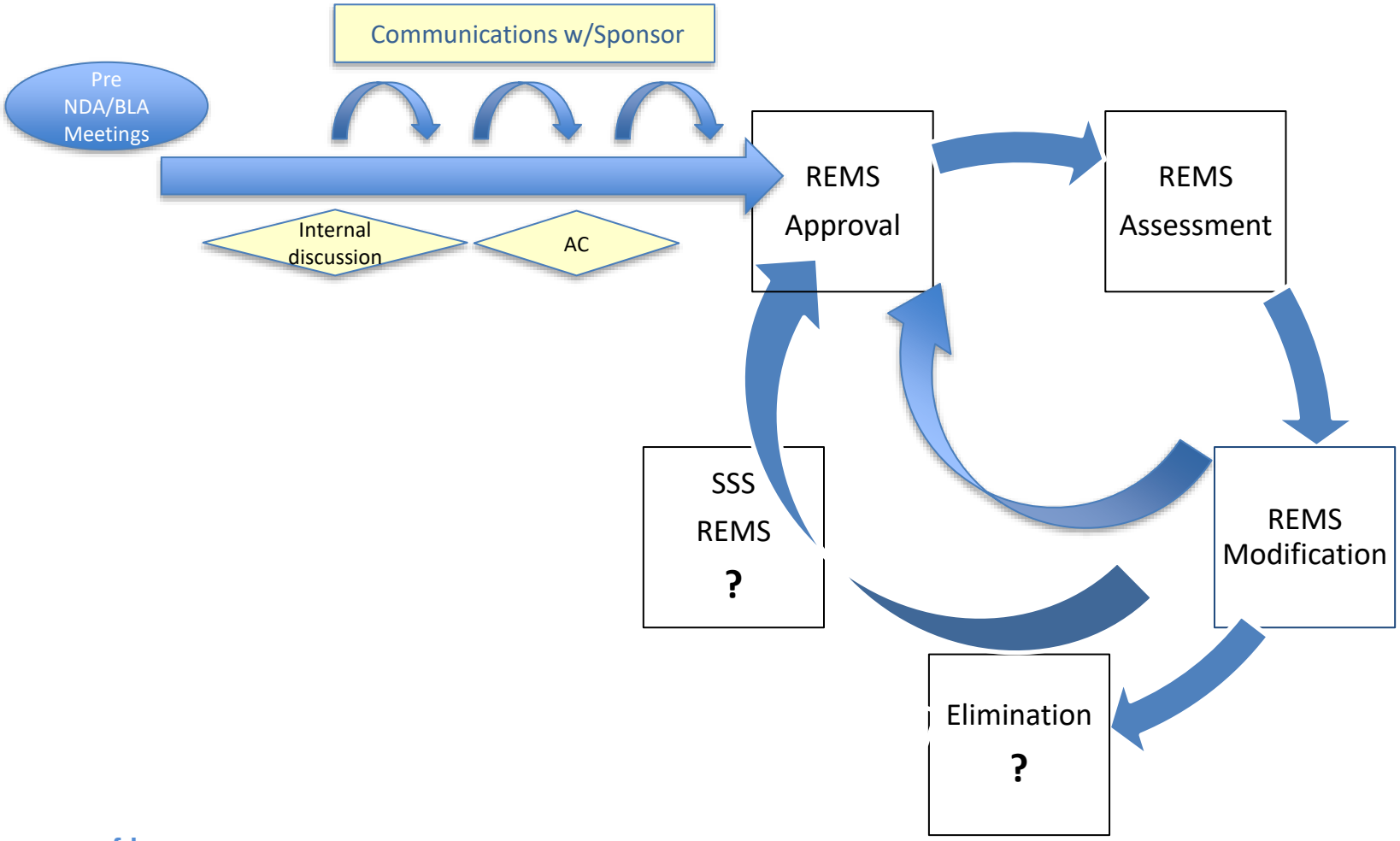
- REMS Document
- REMS Materials (Enrollment Forms, Patient Guides, etc.)
- REMS Supporting Document

The proposed REMS will be reviewed to ensure:

- ✓ the required elements are incorporated
- ✓ the materials are aligned with the label and include necessary elements
- ✓ the supporting document details the operations of the REMS program and ensures the program minimizes burden and patient access issues to the extent practicable.

Post-Approval

Lifecycle of a Product with a REMS



REMS are evaluated for their effectiveness.

- Sponsors are required to submit assessments at pre-determined intervals
  - The minimum timetable for submission of assessments is at a 18 months, 3 year and 7 years after the initial date of approval
- Assessments are used to determine whether the REMS is meeting its goals and/or if modifications to the REMS are necessary

REMS may need to be modified post-approval.

The Agency may require a modification if necessary to ensure the benefits of the drug outweigh risks, minimize burden, or accommodate different, comparable aspects of the ETASU for an ANDA and the applicable RLD.

Sponsors may propose modifications to their REMS programs at any time.

Minor and Major Modifications require a full and complete submission.

Development of a REMS is multidisciplinary

REMS are a highly interactive and iterative process that occurs during the review of the application

Office of New Drugs
Experts in safety & efficacy and indicated condition(s)

Office of Generic Drugs

Office of Medical Policy
OPDP –Review REMS materials for promotional content

Office of Compliance
Review the implementation system and ensuring REMS is enforceable

Risk Specific Experts
Controlled Substance Staff
Pediatric and Maternal Health

Office of Surveillance and Epidemiology

DRM – Provides risk management expertise on the development and implementation of REMS

DMEPA – Experts in safety risks due to medication errors

DPV – Experts in post-marketing drug safety

DEPI – Expertise that contributes to REMS assessment methods & databases

REMS development, modification and assessment is a collaboration involving many CDER divisions and offices

- Pre-market and post-approval design and evaluation involve multiple divisions and offices including New Drugs, Medical Policy, Compliance, Regulatory Policy and Surveillance and Epidemiology.
- Shared System development adds in the expertise of the Office of Generic Drugs and the Office of Regulatory Policy.

Challenge Question #2

Which of the following statements is NOT true?

A. A complete REMS submission includes the REMS document and all appended materials.

B. The appended materials are aligned with the label and include any necessary materials or documentation to operationalize the program.

C. The goals and required elements are determined by the Agency.

D. The Agency may send several IRs to communicate any needed changes to the Sponsor

Resources

- *REMS@FDA*
- *Risk Evaluation and Mitigation Strategies REMS web site.*
- *Drugs@FDA*

QUESTIONS