Risk Evaluation and Mitigation Strategies (REMS) Compliance Program

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Learning Objectives

- Identify the role of FDA's Risk Evaluation and Mitigation Strategies (REMS) Compliance Program
- Identify components of Risk Evaluation and Mitigation Strategies (REMS) Program
- Determine best practices for successful REMS inspections

Agenda

- Overview of FDA's REMS Compliance Program
- Best Practices for REMS Inspections
- REMS Compliance in a Pandemic Situation

Office of Compliance Mission

Mission: To shield patients from poor quality, unsafe, and ineffective drugs through proactive compliance strategies and risk-based enforcement actions.

How we support the Mission:

- Addressing patient health risks that arise from violations of FDA regulations and law
- Developing risk-based enforcement and communication strategies to reduce and prevent patient harm associated with these violations
- Ensuring drugs in FDA approval system have reliable evidence of safety and effectiveness and drugs meet postmarket safety requirements.

https://www.fda.gov/about-fda/center-drug-evaluation-and-research/office-compliance

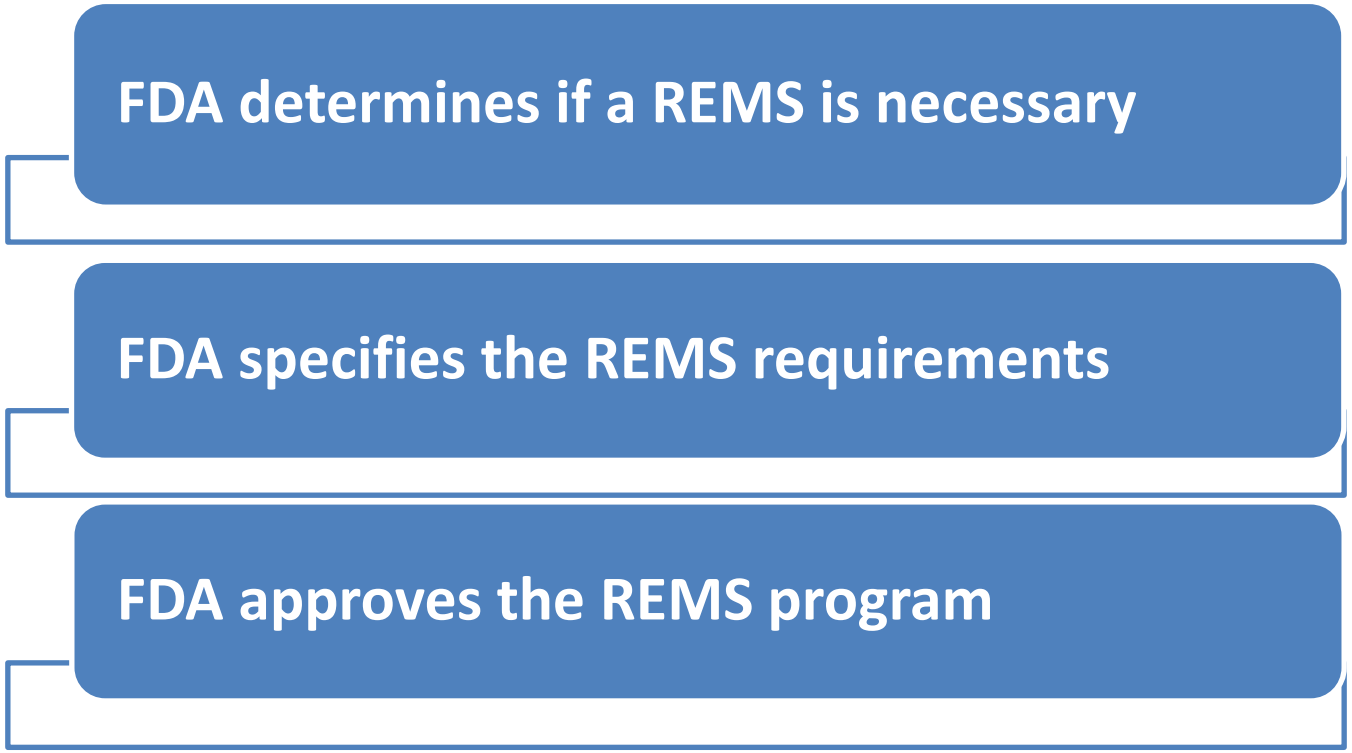
Why does FDA require REMS for a specific drug?

Communicating with Patients

Communicating to Health Care Providers, Pharmacists and Health Care Settings

Required Activities or Clinical Interventions

Who is responsible for developing REMS program?



The applicant is responsible for <u>developing</u> and <u>implementing</u> the REMS program

Legal Framework

There are no regulations for REMS. However, section 505-1 of the Food Drug and Cosmetic Act authorizes FDA to **require REMS.**

We enforce based on this statute.

A REMS may include:

- Medication Guide (MG)
- Communication Plan (CP)
- Packaging and safe disposal technologies
- Elements to Assure Safe Use (ETASU)
- Implementation System (IP)

Approved Risk Evaluation and Mitigation Strategies (REMS)

~ 286 REMS programs have been approved since 2008.

Information regarding currently approved individual and shared systems REMS can be found at REMS@FDA website.

https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsData.page

60 REMS (currently active)

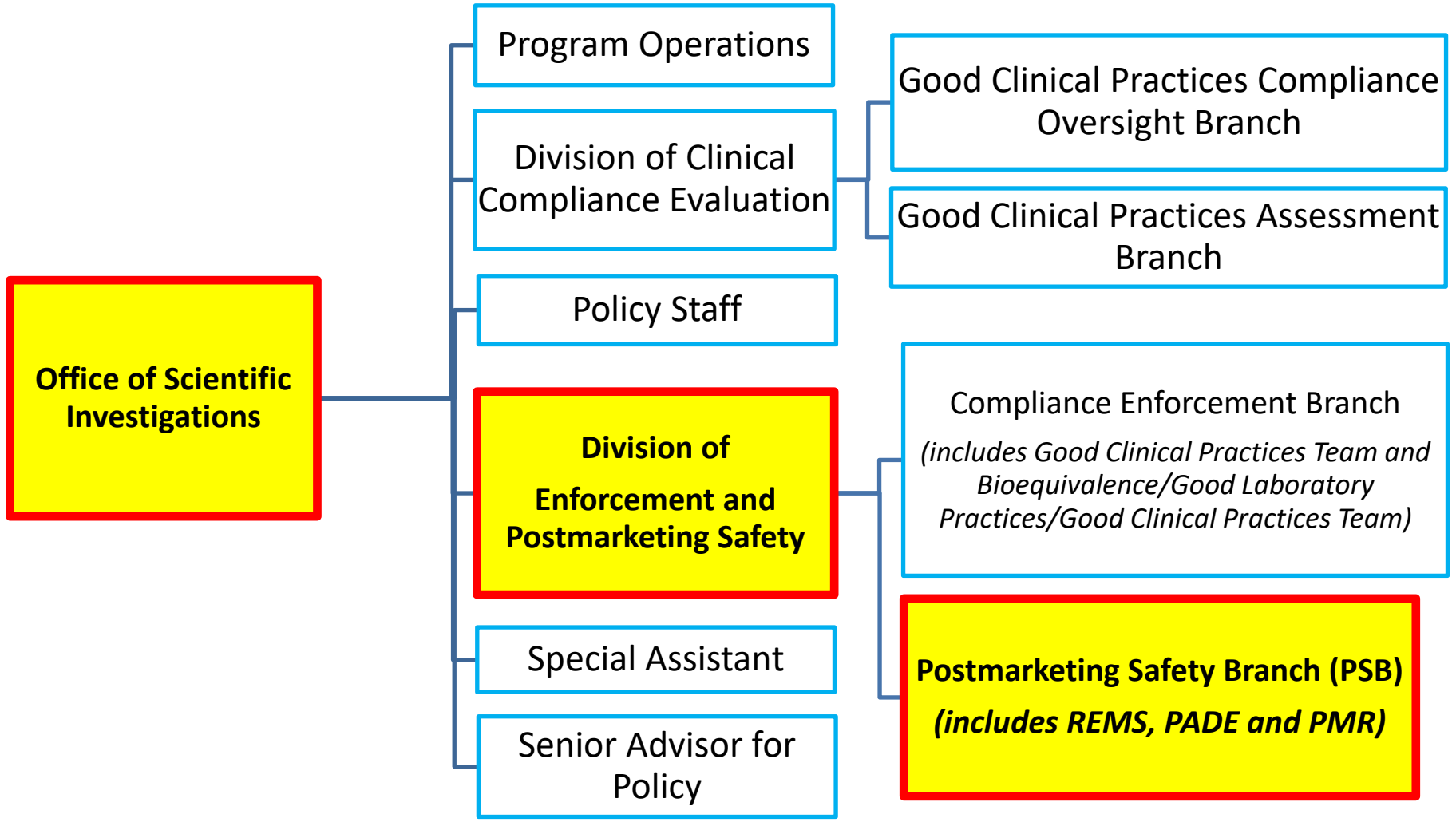
- 52 [87%] include “elements to assure safe use” (ETASU).
- 5 [8%] include only a "communication plan" REMS element which is informational in nature.
- 1 [2%] include only the “medication guide" REMS element.
- 2 [3%] include the "communication plan" AND "medication guide" REMS elements only.

https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsData.page

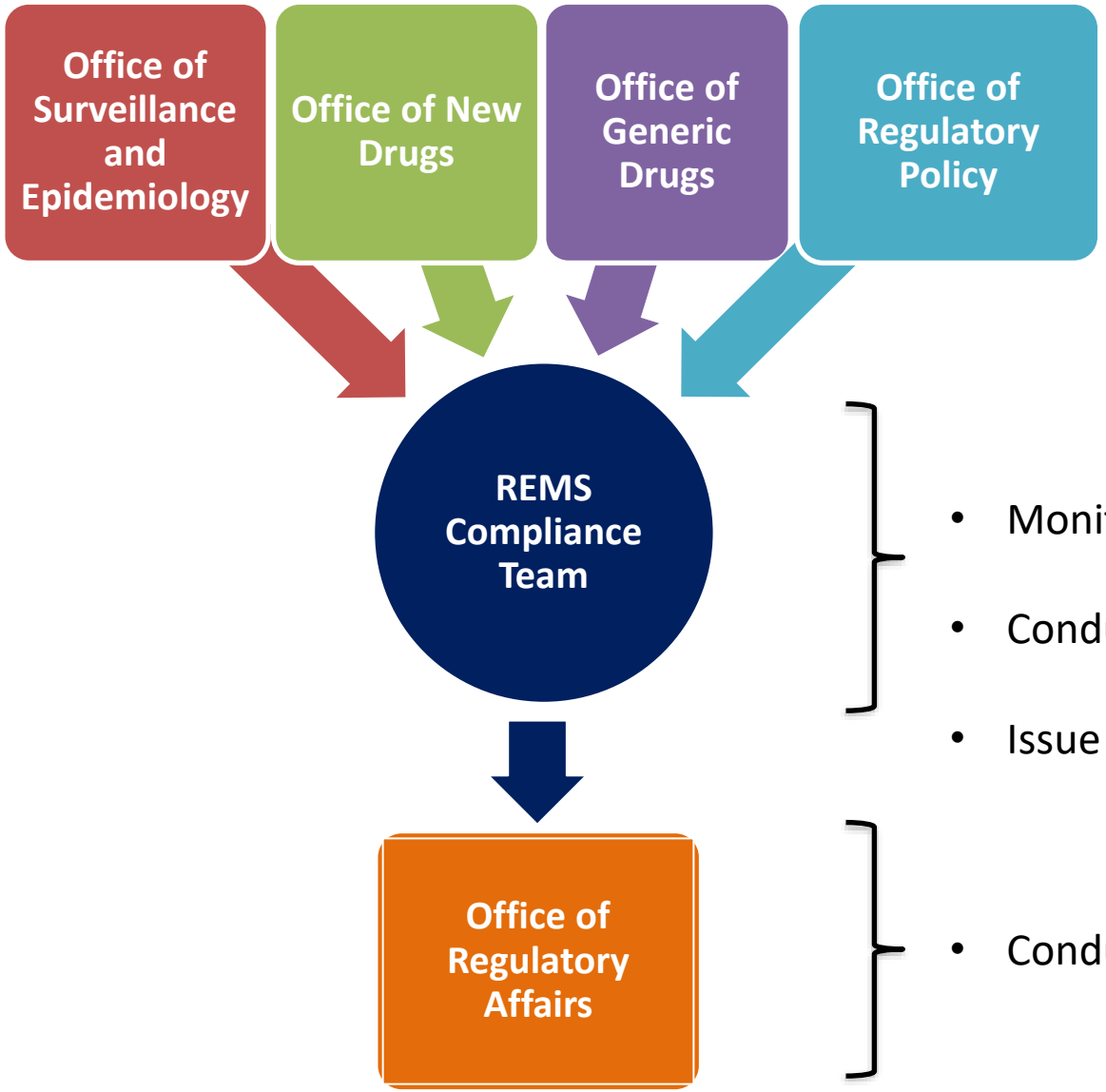
13 Active Shared System REMS Programs

- Encompasses multiple prescription drugs (e.g., RLD and generics) or biologic products or a class of drug or biologic products
- Can involve multiple NDAs, BLAs, and/or ANDAs
- Developed and implemented jointly by two or more applicants
- Includes a single REMS document, REMS materials (except MGs), and supporting documents agreed to by all applicants and approved as part of each application
- Applicants generally share in the implementation and maintenance of any database and infrastructure

Office of Compliance Organization Relevant to Postmarketing Safety



Office Collaboration



- Analyze REMS information to protect and promote public health
- Identify potential REMS compliance concerns

- Monitor industry compliance
- Conduct risk assessments
- Issue REMS inspections

- Conduct REMS inspections

REMS Compliance Program Objectives

- Assure safe and effective human drugs are available
- Verify accuracy, reliability, and timeliness of REMS information submitted to FDA
- Support internal stakeholders by ensuring that REMS materials are submitted
- Monitor industry compliance with REMS requirements

NDAs and BLAs must include a timetable for submission of REMS Assessments

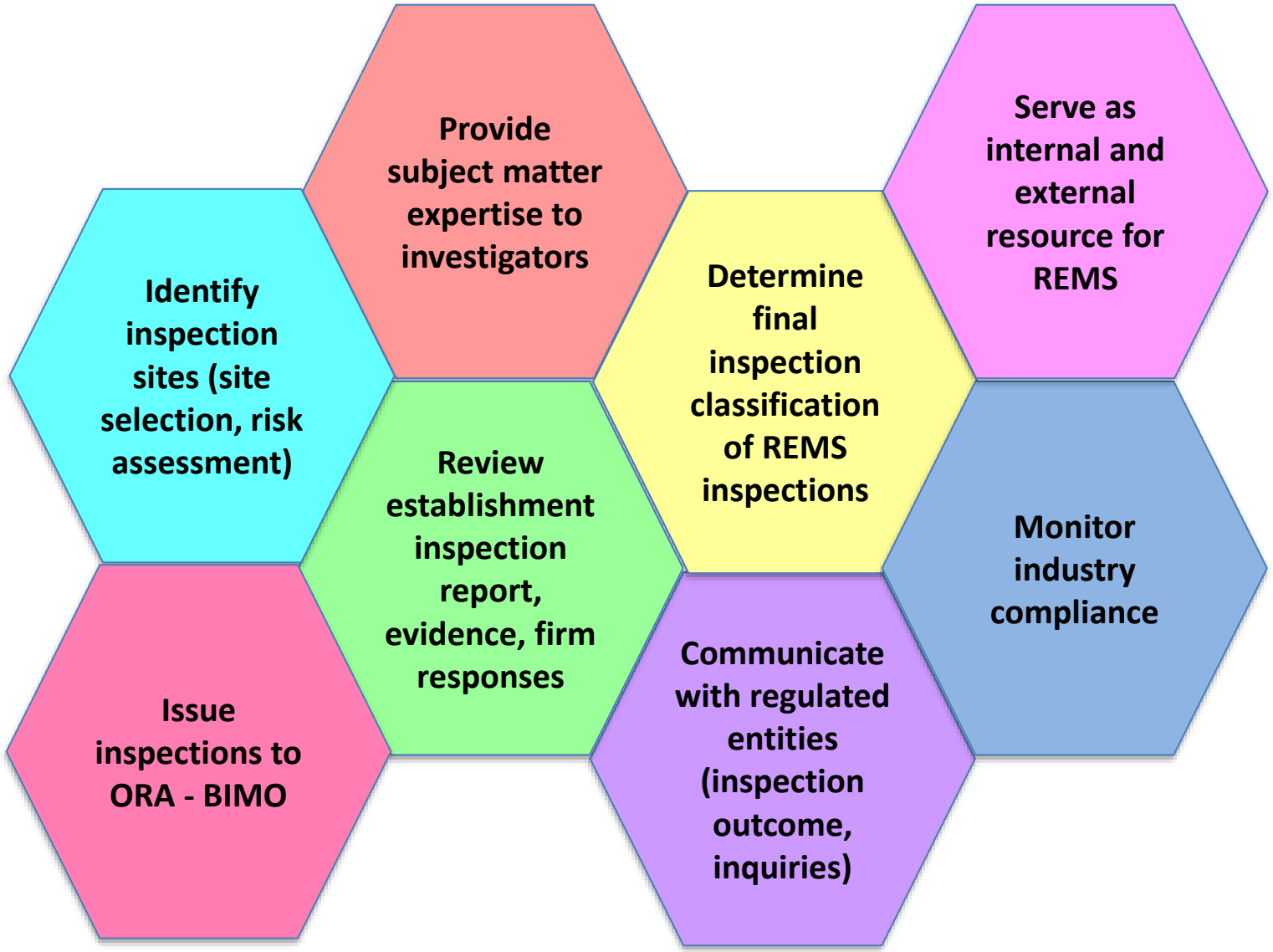
- Assessments **must** be submitted at a minimum of 18 months, 3 years, and 7 years after the REMS is approved
- Approximately 50 REMS Assessment Programs are reviewed annually

REMS Modifications

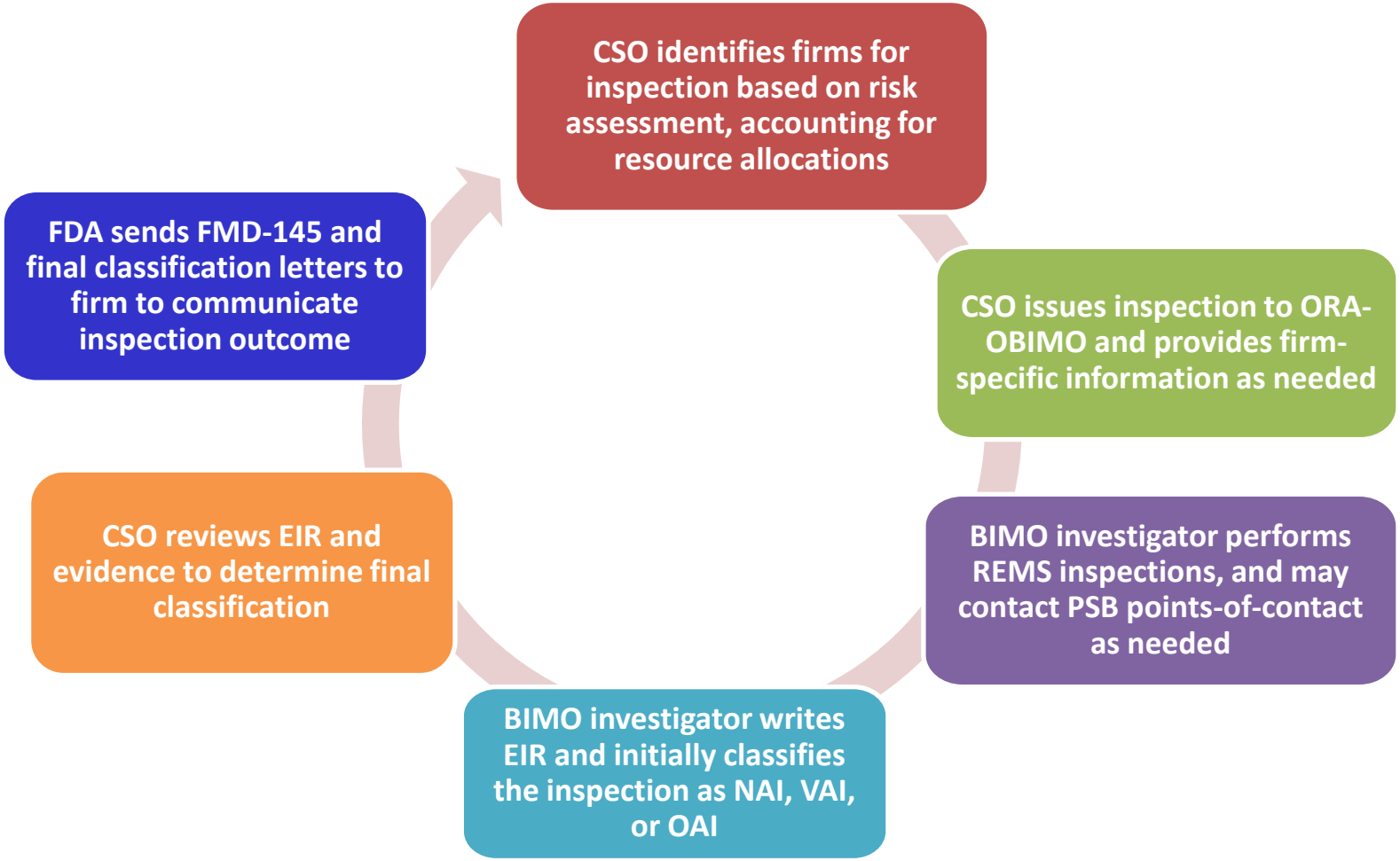
The REMS Compliance Team provides comments for modifications to the REMS in conjunction with:

- Office of New Drugs (OND)
- Office of Surveillance and Epidemiology (OSE) - Division of Risk Management (DRM)

REMS Inspection Activities



REMS Inspection Process



REMS INSPECTIONS

Who do we Inspect?

- Sponsor/Application Holders
- Applicant's contractors

Applicant retains statutory obligation to ensure the REMS functions in accordance to the approved REMS

Site Selection
Risk-based approach

- REMS with ETASU that have never been inspected
- REMS with ETASU with issues from previous inspection
- REMS with ETASU that was modified since last inspection
- REMS with communication plans that have never been inspected
- Input from other Offices

REMS with Med Guide

Medication Guide

- Required to be dispensed with the drug
- Determine if distributed to each patient when the drug is dispensed

What we collect

- Copy in the version or format provided to each patient
- Copy of patient package inserts provided to each patient

REMS Inspections with a Communication Plan

- Verify the distribution dates of the Communication Plan were in accordance with the dates provided in the REMS document
- Verify professional journal communication was in the journal as per the dates provided in the REMS document
- Verify communication plan is available on REMS website, if applicable

What we collect

- Communication materials distributed
- Copy of the communication information from professional journals, along with the dates, volume, and issue
- Dates the REMS information was presented at Scientific Meetings

Elements to Assure Safe Use

Elements to Assure Safe Use may have **1 or more** elements to mitigate the known serious risks associated with the use of the drug.

- Element A: Healthcare Providers
- Element B: Pharmacies
- Element C: Certain Healthcare Settings
- Element D: Documentation of Safe Use
- Element E: Monitoring
- Element F: Registry

What do we collect

- Documentation of compliance with requirements to become certified – e.g., training, program enrollment, etc.
- Documentation of pharmacy, practitioners or healthcare settings certification process
- Documentation of a validated, secure database of certified pharmacies, practitioners or healthcare settings
- Documentation of applicant’s activities related to surveillance of the risks addressed by REMS program

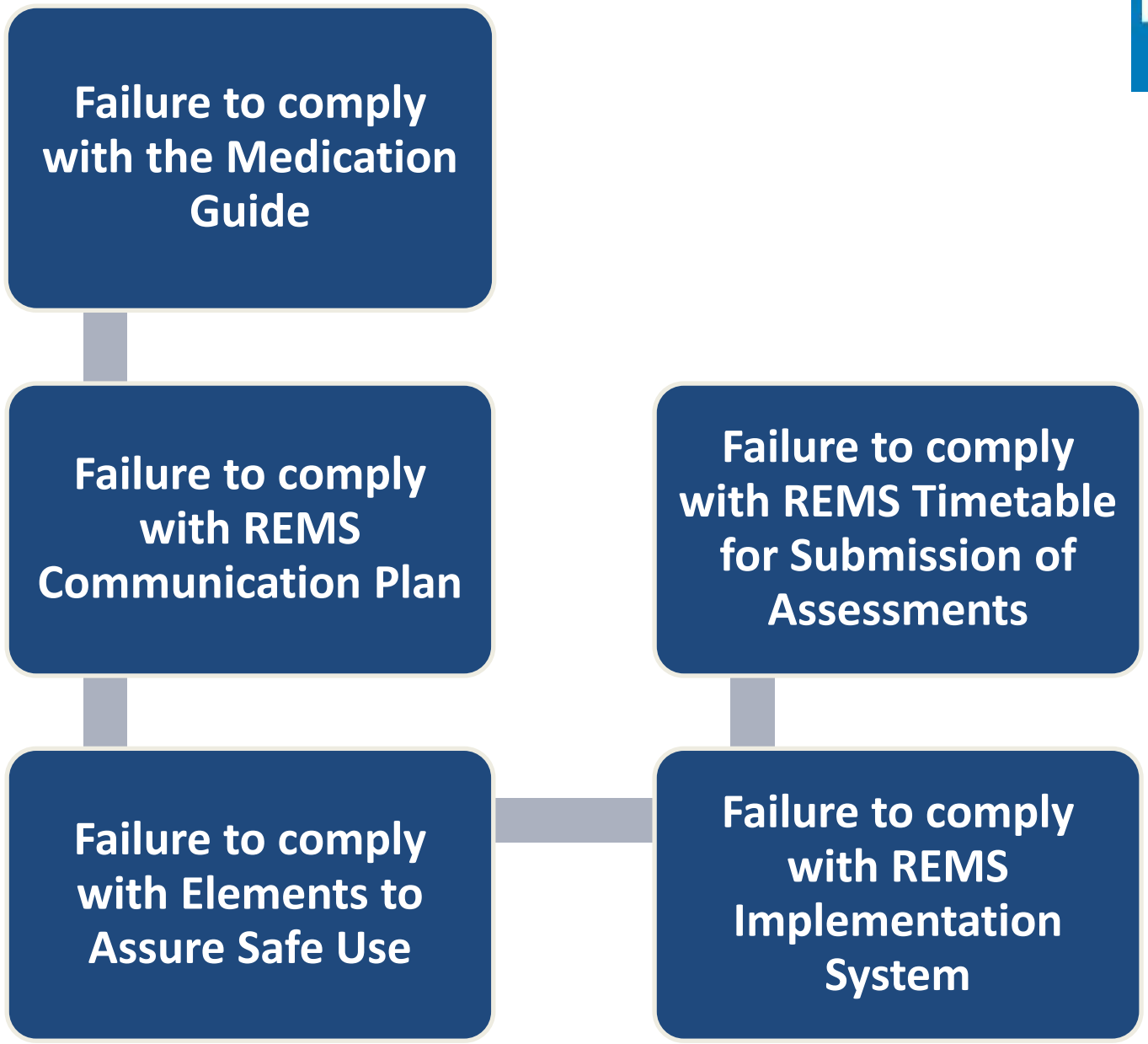
What do we collect (cont)

- Documentation of safe use conditions as described in the approved REMS
- Documentation that Applicant identifies and addresses non-compliance
- Documentation of maintenance of a validated, secure database
- Documentation of REMS Program Call Center activities

REMS Inspection Classifications

NAI	• **No Action Indicated** • No objectionable conditions or practices found or the objectionable conditions found do not justify further regulatory action
VAI	• **Voluntary Action Indicated** • Objectionable conditions or practices found, but the agency is not prepared to take or recommend any administrative or regulatory action
OAI	• **Official Action Indicated** • Regulatory and/or administrative actions will be recommended

Possible Inspection Observations/ Citations



Best Practices for Inspections

- Establish clear and concise inspection procedures
- Make key documents and records accessible and available
- Compile complaints and Corrective and Preventive Actions (CAPAs) since your last inspection
- Report all corrections and keep documentation current

Possible Enforcement Action

- Warning letters
- Impose civil monetary penalties for violations of the FD&C Act - 303(f)(4)
- Seizure of the drug subject to the REMS
- Injunction

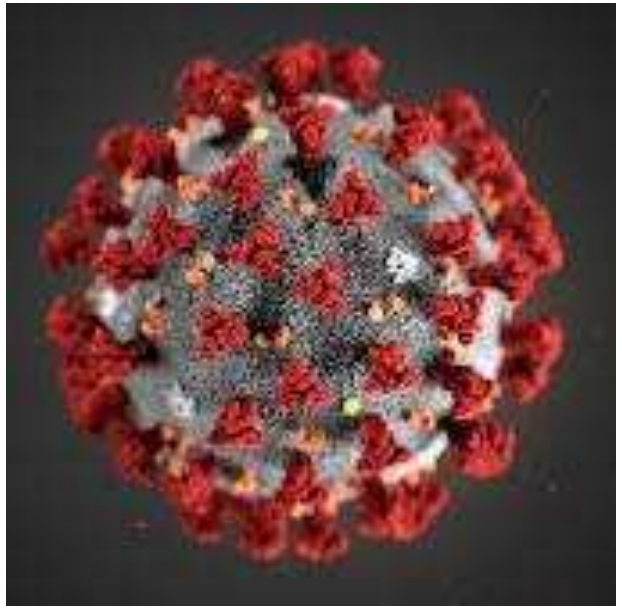
REMS Compliance: Pandemic

During Pandemic

FDA expects applicants to maintain compliance for products

If unable:

1. The applicant **must document**
2. The applicant **must notify**
3. The applicant **must maintain documentation**



Post-Pandemic

Resume compliance with REMS program

REMS Compliance: Pandemic

FDA has issued guidance to communicate its temporary policy for certain risk evaluation and mitigation strategies (REMS) requirements for the duration of the public health emergency (PHE) declared by the Secretary of Health and Human Services (HHS) on January 31, 2020.

Guidance document available:

Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

https://www.fda.gov/media/136317/download

Challenge Questions

Question 1: Which of the following elements <u>can</u> be included in a REMS? Select all that apply.

A. Medication Guide

B. Prescription drug plan

C. Communication Plan

D. Elements to Assure Safe Use (ETASU)

E. Implementation System

F. Financial records

Question 2: Which item is not a REMS Compliance Team activity?

A. Provide subject matter expertise to investigators
B. Determine final inspection classification of REMS inspections
C. Identify inspection sites (site selection, risk assessment)
D. Provide labeling to stakeholders

Question 3: After approval, REMS Assessments must not be submitted at a minimum of:

A. 18 months

B. 3 years

C. 7 years

D. Every June and December

Resources

Risk Evaluation and Mitigation Strategy Compliance Program: FD&C Act Chapter V: Drugs and Devices
https://www.fda.gov/regulatory-information/federal-food-drug-and-cosmetic-act-fdc-act/fdc-act-chapter-v-drugs-and-devices

REMS Guidance-Format and Content of a REMS Document
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/format-and-content-rems-document-guidance-industry

Medication Guides Distribution Requirements and Inclusion in REMS
https://www.fda.gov/drugs/drug-safety-and-availability/questions-and-answers-guidance-industry-medication-guides-distribution-requirements-and-inclusion

REMS@FDA Website
http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Risk Evaluation and Mitigation Strategies: Modifications and Revisions – Guidance for Industry (June 2020)
https://www.fda.gov/media/128651/download

REPORT: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS) (Sept 2014)
https://www.fda.gov/media/89860/download

FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry
https://www.fda.gov/media/100307/download

Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals
https://www.fda.gov/media/136317/download

Conclusion

- **No regulations**; enforce based on statute
- REMS can be for a single drug or a class of drugs
- Each REMS is unique (i.e., no two REMS are alike)
- Document activities related to REMS Inspections
- Documentation is important to REMS inspections

For Questions

REMS Compliance Team mailbox:

CDER-OSI-REMS@fda.hhs.gov

REMS Compliance Program:

https://www.fda.gov/media/111789/download

40