Session 2:
REMS Inspections

Risk Evaluation and Mitigation Strategy (REMS) Inspections

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Objectives

- Provide an overview of the REMS program to help Applicants prepare for BIMO REMS Inspections

- Provide best practices to address inspection findings

Agenda

- Overview of REMS Elements

- Shared System REMS

- The REMS Inspection Process

- Best Practices to Address Inspection Findings

- REMS Specific Issues

- Preparing for REMS Inspections

What is a REMS?

- **R**isk **E**valuation and **M**itigation **S**trategy

- A required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks

REMS

- FDAAA, Title IX, Subtitle A, section 901, created new section 505-1 of the Act authorizing FDA to require REMS

- Drug and biologic applicant holders develop REMS programs, FDA reviews and approves them

- REMS programs can be used 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
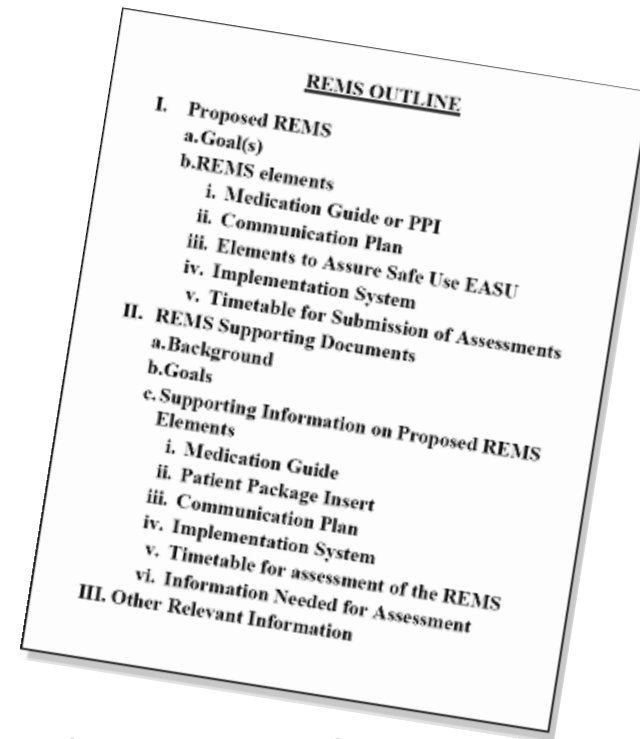
REMS Are Enforceable

- REMS must be fully operational before drug introduced into interstate commerce

- Drug may be found to be misbranded (502(y))

- FDA can impose civil monetary penalties for violations of the FD&C Act - 303(f)(4)

Risks REMS Aim to Mitigate

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Example of Risk	Potential REMS action to Mitigate Risk
Serious Infection	Patient education of warning signs of infection prior to prescribing drug
Severe allergic reaction	Healthcare professional must be certified to administer the drug
Liver damage	Monitor liver function while the patient is using the drug
Severe birth defects	Negative pregnancy test prior to dispensing the drug

A REMS **may** include:

- Medication Guide (MG)

- Communication Plan (CP)

- Elements to Assure Safe Use (ETASU)

- Implementation System

REMS OUTLINE

I. Proposed REMS
  a. Goal(s)
  b. REMS elements
    i. Medication Guide or PPI
    ii. Communication Plan
    iii. Elements to Assure Safe Use EASU
    iv. Implementation System
    v. Timetable for Submission of Assessments
II. REMS Supporting Documents
  a. Background
  b. Goals
  c. Supporting Information on Proposed REMS Elements
    i. Medication Guide
    ii. Patient Package Insert
    iii. Communication Plan
    iv. Implementation System
    v. Timetable for assessment of the REMS
    vi. Information Needed for Assessment
III. Other Relevant Information

A REMS must include:

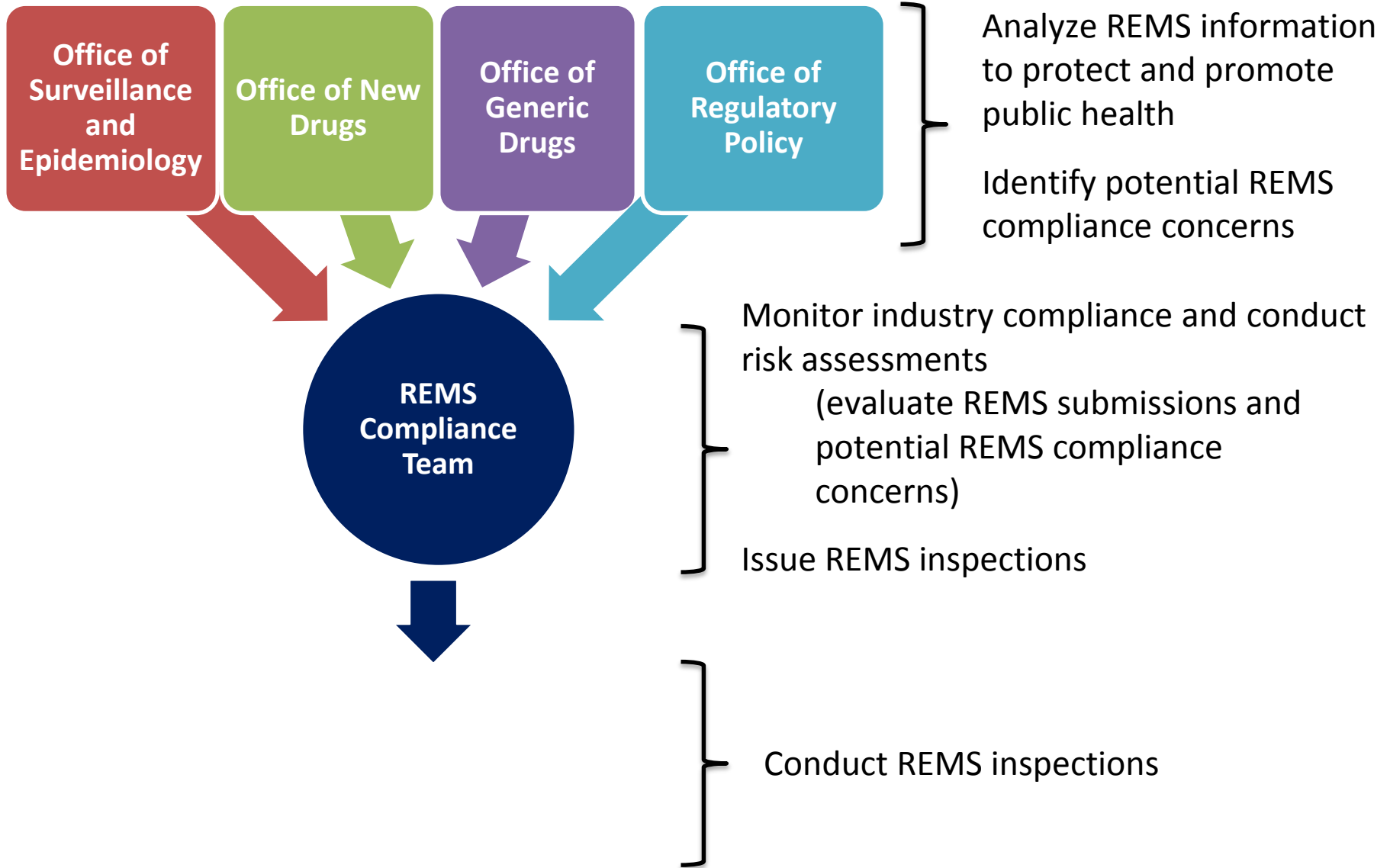- Timetable for submission of assessments

Shared System REMS

- Developed for a single drug or biologic product or a class of drug or biologic products

- Includes NDAs and ANDAs

- Single REMS document, REMS materials (except MGs), and supporting documents applicable to all drugs

- Shared database and infrastructure

Shared System REMS

FDA

Examples of Shared System REMS:

- Isotretinoin – iPLEDGE Program

- Extended-Release and Long-Acting (ER/LA) Opioid Analgesics

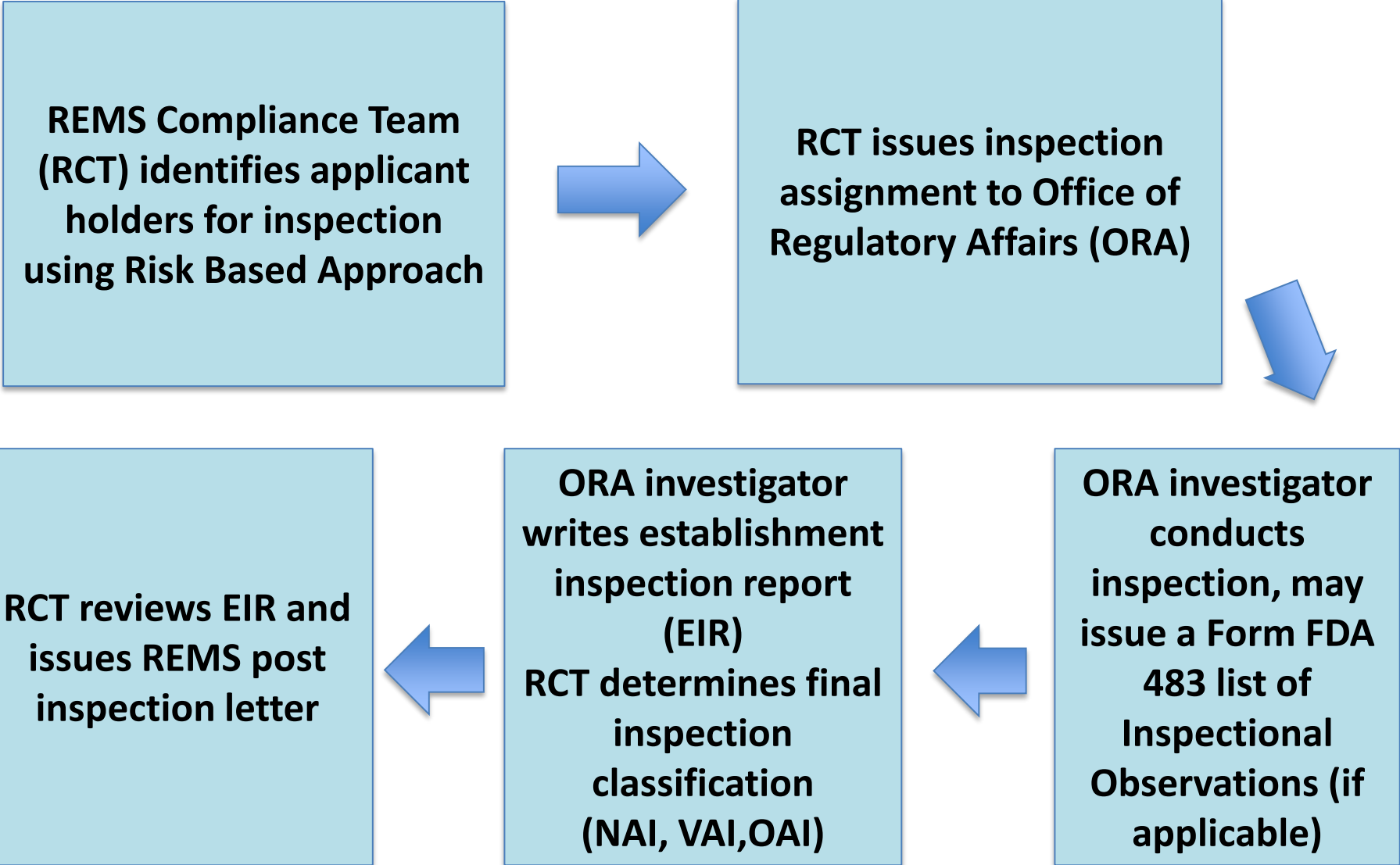- Buprenorphine Transmucosal Products for Opioid Dependence (BTOD)

FDA Use of REMS Information

Office of Surveillance and Epidemiology

Office of New Drugs

Office of Generic Drugs

Office of Regulatory Policy

Analyze REMS information to protect and promote public health

Identify potential REMS compliance concerns

REMS Compliance Team

Monitor industry compliance and conduct risk assessments
(evaluate REMS submissions and potential REMS compliance concerns)

Issue REMS inspections

Conduct REMS inspections

ORA and CDER Work Together

REMS Inspection Process

FDA

REMS Compliance Team (RCT) identifies applicant holders for inspection using Risk Based Approach

→

RCT issues inspection assignment to Office of Regulatory Affairs (ORA)

↘

RCT reviews EIR and issues REMS post inspection letter

←

ORA investigator writes establishment inspection report (EIR)
RCT determines final inspection classification (NAI, VAI, OAI)

←

ORA investigator conducts inspection, may issue a Form FDA 483 list of Inspectional Observations (if applicable)

Purpose of a REMS Inspection

- Verify the REMS is implemented and functioning in accordance to the FDA approved REMS

- Verify information in the REMS assessment report

How do we select REMS to be Inspected?

Site Selection – Risk based approach

- REMS with ETASU never inspected

- REMS with ETASU – issues during previous inspection

- REMS with ETASU – modified since last inspection

- REMS with Communication plans – never inspected (after assessment received if possible)

- REMS – requests from OND/OSE

Possible Inspection Sites

- Sponsor/Applicant

- Call Center

- Vendor/Contract Research Organization

Contractor Inspections

- REMS inspections may be conducted at the Applicant's contractors

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

Contractor Information Collected

- Copy of the contract (financial information may be omitted)

- List of the subcontractors

- Description of the processes or functions performed by the contractor for the REMS program

- Records pertaining to the REMS that are held by the contractor

- REMS training records or standard operating procedures

REMS Inspections Conducted, by Fiscal Year
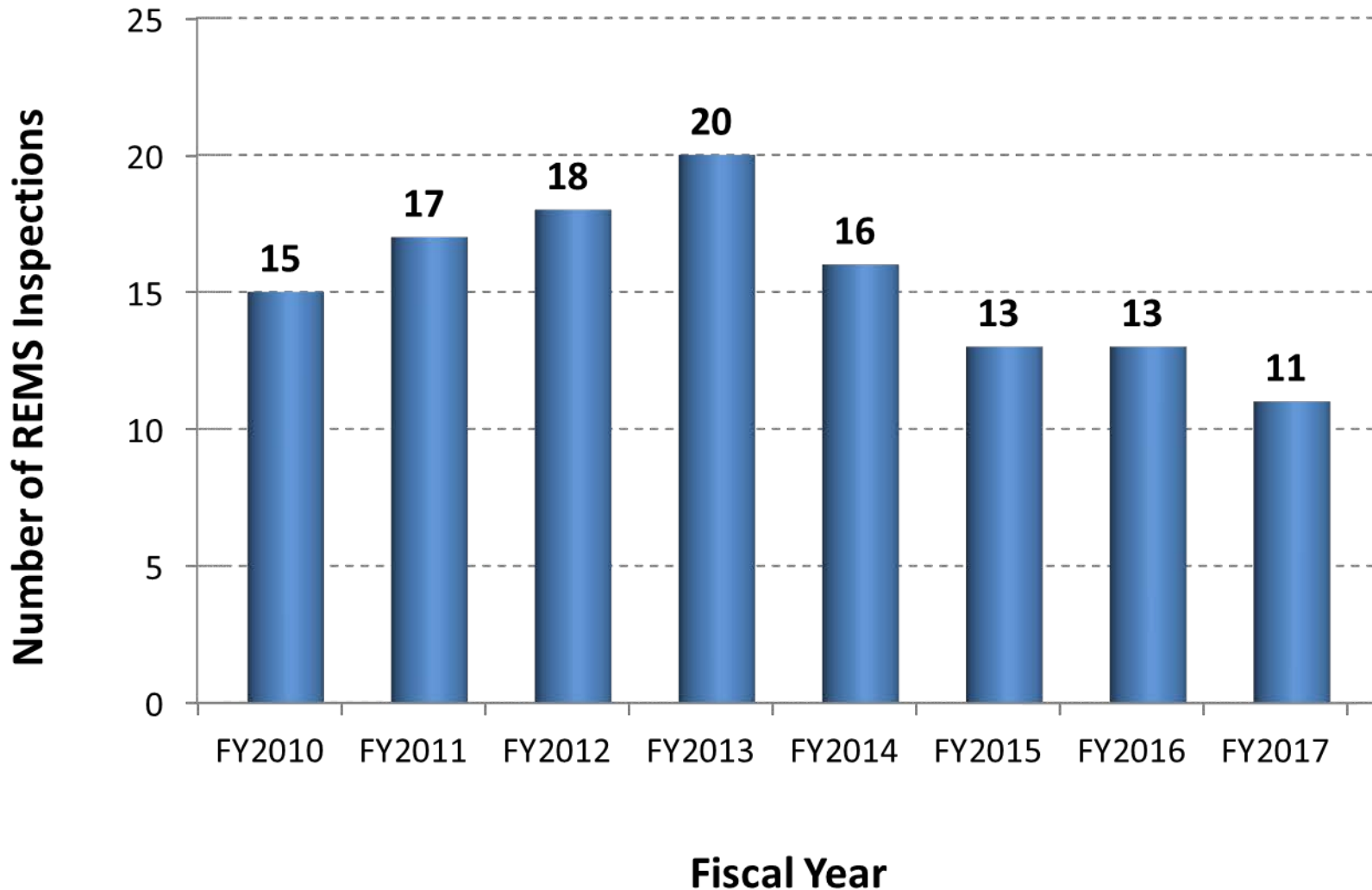
Inspection Classifications

- **No Action Indicated (NAI)**

  - No objectionable conditions or practices

- **Voluntary Action Indicated (VAI)**

  - Objectionable conditions or practices
  - Not at threshold to take or recommend administrative or regulatory action

- **Official Action Indicated (OAI)**

  - Significant objectionable conditions found
  - Regulatory action recommended

General Information Collected

1. Date the *XYZ* REMS was operational and the date of product launch

2. List of all contractors associated with the *XYZ* REMS to include the point of contact, street address, and phone number of each contractor

3. Contracts with specifications of the contractor's responsibilities

4. Written procedures and training materials
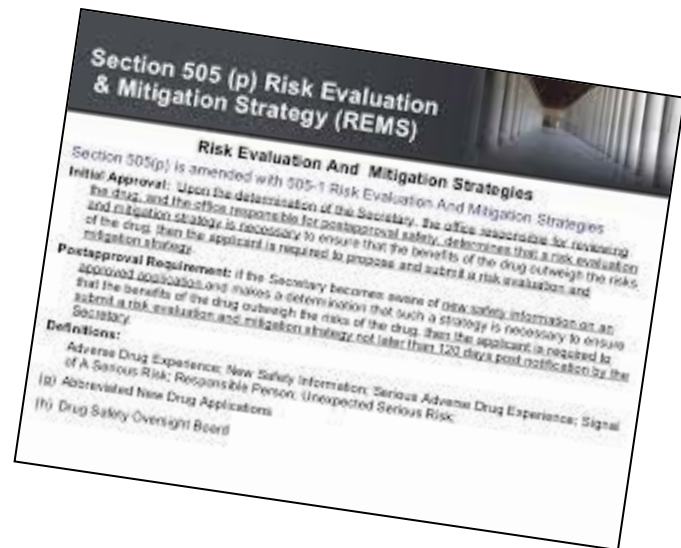
5. Organizational charts

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Reviewer, REMS Compliance Team

Medication Guides as part of REMS

Medication Guides that are required as part of REMS under Section 505-1 are subject to the assessment and modification provisions of Section 505-1(g) and (h) of the FD&C Act.

Medication Guides

- Required to be dispensed with the drug

- Written in non-technical language

- Standardized format (font size, headers, etc.)

- Provided in ***addition** to* general information sheets (Consumer Medication Information or CMI)

What we look for during an Inspection

1. Is the Medication Guide being distributed to each patient when the drug is dispensed?

2. We collect a copy of the Medication Guide in the version or format (hardcopy) that is provided to each patient
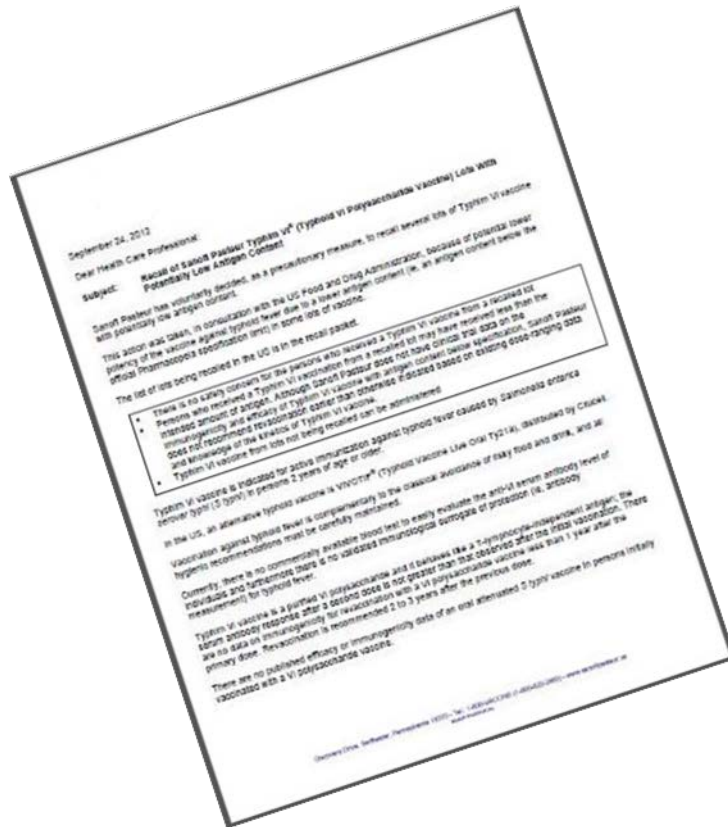
Communication Plan

A Communication Plan is:

- Developed by the applicant holder to support

- implementation of an element of the REMS, and Can inform key audiences (e.g., healthcare providers) about the risk of the drug

Communication Plans can include

Sending letters to Healthcare Providers (e.g., Dear Healthcare Provider letters)

Communication Plans can include

- Disseminating information through professional societies about any serious risks of the drug and any measures to assure safe use

A communication plan educates, informs, and raises awareness of risk.

What we look for during an Inspection

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1. Were the distribution dates of the Communication Plan in accordance with the dates provided in the REMS document?

2. Were the professional journal communications in the journal as per the dates provided in the REMS document?

3. Is the communication plan available on the REMS website, if applicable?

Possible FDA 483 items for Inspections with a Communication Plan

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1. Communication Plan was not distributed to required health care providers, professional societies, etc.

2. Communication Plan was distributed late

3. Not distributing letters to healthcare providers (e.g., Dear Healthcare Provider letters)

Elements To Assure Safe Use

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- Elements to Assure Safe Use (ETASU) may be required to provide safe access for patients to drugs with known serious risks due to inherent toxicity or potential harmfulness

- ETASU is a strategy to mitigate a specific serious risk listed in the labeling of the drug

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
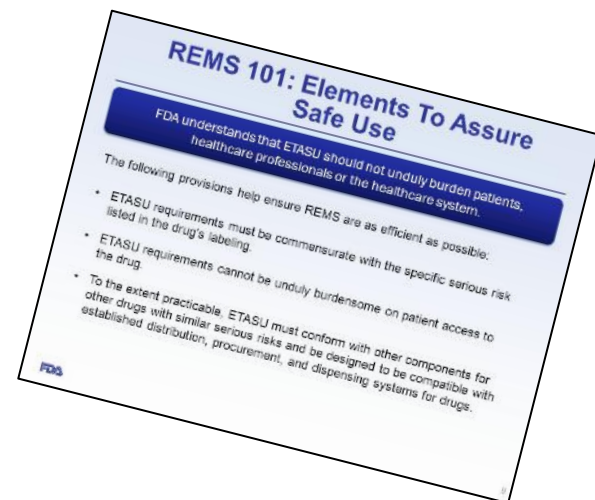
Element A

Healthcare providers who prescribe the drug have particular training or experience, or are specially certified. (section 505-1(f)(3)(A))

Examples:

Education program for prescribers

- ER/LA opioid analgesics REMS

Training

- Qsymia REMS

Specially certified

- Caprelsa REMS

- Isotretinoin REMS

Element A: What we look for during an Inspection

FDA

- Number of healthcare providers that have received training

- Healthcare provider certification is documented

- Documentation of applicant's activities related to surveillance of the risks addressed by REMS program

- Applicant identifies and addresses non-compliance

Element B

Pharmacies, practitioners, or health care setting that dispense the drug are specially certified. (section 505-1(f)(3)(B))

Examples:

Pharmacy

- Clozapine REMS

Healthcare setting

- Lemtrada REMS

Element B: What we look for during an Inspection

FDA

- 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

- Mechanism that applicant uses to identify and address non-compliant certified pharmacies, practitioners or healthcare settings

- Applicant identifies and addresses non-compliance

Element C

Drug dispensed to patients only in certain health care setting, such as hospitals

(section 505-1)(f)(3)(C))

Example:

- Aveed REMS

Element C: What we look for during an Inspection

- Documentation that the drug is shipped only to certified facilities

- Documentation of healthcare setting or wholesalers/distributors enrollment process

- Documentation of the applicant's activities related to compliance with REMS program

- Applicant identifies and addresses non-compliance

Element D

Drug dispensed to patient with evidence or other documentation of safe-use conditions, such as laboratory test results (section 505-1)(f)(3)(D)

Examples:

Patient Enrollment Form

- Tracleer REMS
- Clozapine REMS

Laboratory tests

- Isotretinoin REMS

Element D: What we look for during an Inspection

FDA

- Documentation of safe use conditions as described in the approved REMS

- Documentation of REMS Program Call Center activities

- Documentation of maintenance of a validated, secure database

- Applicant identifies and addresses non-compliance

Element E

Each patient using the drug is subject to certain monitoring (section 505-1(f)(3)(E))

Example:

- Clozapine REMS

Element E: What we look for during an Inspection

- Documentation of patient monitoring according to the requirements of the approved REMS

- Documentation of pharmacy, practitioner, patient, or healthcare setting non-compliance

- Applicant identifies and addresses non-compliance

Element F

Each patient using the drug is enrolled in a registry (section 505-1(f)(3)(F))

Example:

Pregnancy registry

- Isotretinoin REMS
- Mycophenolate REMS

Element F: What we look for during an Inspection

- Verify that the registry is in place and all patients are enrolled in a registry

- Documentation of patient registry enrollment non-compliance

- Applicant identifies and addresses non-compliance

Implementation System

To assure safe use, elements B, C and D may include a system through which the applicant is able to take reasonable steps to monitor and evaluate implementation of such elements and work to improve them

Implementation System: What we look for during an Inspection

- Documentation of all processes and procedures to support REMS requirements

- Documentation and maintenance of a validated, secure database of all certified stakeholders in the REMS Program

- Documentation and maintenance of a REMS Program Call Center and a REMS Program website

- Documentation of audits and an ongoing audit plan

- Applicant identifies and addresses non-compliance

Possible Enforcement Action

- Seizure of the drug subject to the REMS

- Injunction

- Civil Monetary Penalties
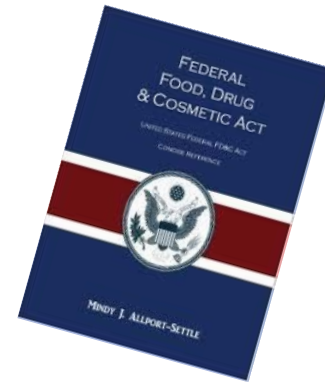
REMS: Key Points

- The REMS CP is on the FDA's [BIMO Compliance Program Webpage](#)

- REMS can be for a single drug or a class of drugs

- Each REMS is unique (i.e., no two REMS are alike)

Email for REMS Compliance:
CDER-OSI-RMP@fda.hhs.gov

Resources

- **FD&C Act Chapter V: Drugs and Devices**

  http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmetic ActFDCAct/FDCActChapterVDrugsandDevices/default.htm

- **REMS Guidances**

  – **Format and Content of a REMS Document**

    https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf

  – **Medication Guides Distribution Requirements and Inclusion in REMS**

    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc es/UCM244570.pdf

- **REMS@FDA Website**

  http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Resources

- **Risk Evaluation and Mitigation Strategies: Modifications and Revisions – Guidance for Industry (April 2015)**

  http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm441226.pdf

- **REPORT: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS) (Sept 2014)**

  http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf

- **Risk Evaluation and Mitigation Strategies Compliance Program Manual**

  https://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614