CHAPTER 53 – POST-MARKETING SURVEILLANCE AND EPIDEMIOLOGY: HUMAN DRUG AND THERAPEUTIC BIOLOGICAL PRODUCTS

SUBJECT: RISK EVALUATION AND MITIGATION STRATEGIES (REMS) DATE REPORTING INSPECTIONS	IMPLEMENTATION 02/01/2020
DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
Product code for REMS reporting inspection is 66YDY99	53001C I Risk Evaluation and Mitigation Strategies Center Initiated

FIELD REPORTING REQUIREMENTS

Consult your supervisory investigator, the CDER REMS Compliance Team at CDER-OSI-REMS@fda.hhs.gov, or the REMS Compliance Team Consumer Safety Officer (CSO) point of contact (POC) listed in the assignment memorandum, if there are questions or concerns prior to documenting any observations on a Form FDA 483.

Complete all EIRs in accordance with FMD# 86, Establishment Inspection Report (EIR) Conclusions and Decisions (https://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf). Send a copy of the Form FDA 483, "Inspectional Observations" (483), if issued, to the REMS Compliance Team at CDER-OSI-REMS@fda.hhs.gov and the REMS Compliance Team CSO POC via email within three business days of inspection closeout.

Once the EIR has been uploaded and endorsed in eNSpect, please contact the REMS Compliance Team at CDER-OSI-REMS@fda.hhs.gov.

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PART I – BACKGROUND

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA) (Public Law 110-85). Title IX, Subtitle A, section 901 of the statute created a new section 505-1 of the Federal Food, Drug, and Cosmetic Act (the Act), which authorizes FDA to require persons submitting or holding certain applications (responsible person)[1] to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) as part of such application, if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks (section 505-1(a)). Applications that were originally approved without a REMS are required to submit a proposed REMS if FDA becomes aware of new safety information as defined in 505-1(b)(3), and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug (section 505-1(a)(2)). Section 505-1 applies to applications for approval of prescription drugs submitted under sections 505(b) or 505(j) of the Act, and applications submitted under section 351 of the Public Health Service Act. These applications are termed covered applications, and refer to new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs).

In determining whether a drug requires a REMS, section 505-1(a)(1) provides the following factors to consider:

(A) The estimated size of the population likely to use the drug involved.

(B) The seriousness of the disease or condition that is to be treated with the drug.

(C) The expected benefit of the drug with respect to such disease or condition.

(D) The expected or actual duration of treatment with the drug.

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

(F) Whether the drug is a new molecular entity.

The responsible person submits, and FDA approves, a REMS document and appended materials.

The FDA can require different tools, as defined in section 505-1(e), to mitigate the risks of the drug and attain the goals of the REMS. These tools include information for patients, including medication guides as defined under 21 CFR 208, and patient package inserts (section 505-1(e)(2)). A REMS may also include a communication plan (section 505-1(e)(3)) to inform healthcare providers, either directly or through professional societies, about the REMS and encourage implementation of, or explain the risks or safety protocols of, the REMS. If the tools specified under section 505-1(e) of the Act are not deemed adequate to mitigate the risk, FDA may require more restrictive measures, termed elements to assure safe use (ETASU) (section 505-1(f)(3)). The ETASU may include any of the following:

[1] Section 505-1(b)(7) of the Act

(A) Healthcare providers who prescribe the drug have particular training or experience, or are specially certified (the opportunity to obtain such training or certification with respect to the drug shall be available to any willing provider in a widely available training or certification method (including an on-line course or via mail) as approved by the Secretary at reasonable cost to the provider);

(B) Pharmacies, practitioners, or health care settings that dispense the drug are specially certified (the opportunity to obtain such certification shall be available to any willing provider);

(C) The drug be dispensed to patients only in certain health care settings, such as hospitals;

(D) The drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results;

(E) Each patient using the drug be subject to certain monitoring; or

(F) Each patient using the drug is enrolled in a registry.

This Compliance Program (CP) refers to the ETASUs as element A, B, C, D, E, or F for ease of reference.

For REMS that include ETASUs described under 505-1(f)(3)(B),(C), and (D), an implementation system may be required under 505-1(f)(4). Implementation systems generally require that the firm take reasonable steps to monitor and evaluate the implementation of the REMS by healthcare providers, pharmacists, and others in the health care system who are responsible for implementing those elements, and to work to improve their implementation. Additional details about the implementation system are included in the REMS Supporting Document (a document provided by the firm that includes a thorough explanation of the rationale and supporting information for the content of the REMS, but is not part of the approved REMS).

Applicant holders for NDAs and BLAs are required to submit assessments according to intervals set forth in the approved REMS. FDAAA specifies the minimal timeframe (18 months, 3 years, and 7 years) for the submission of assessments from the date of the initial approval of the REMS (section 505-1(d)). FDA provides the applicant holder with a comprehensive assessment plan in their approval letter, addressing the specific content areas in the REMS to include, at a minimum, in their assessment report. The provision for scheduled REMS assessments does not apply to ANDAs (section 505-1(i)(1)).

Assessments are also required when the applicant holder submits a supplemental application for a new indication for use, or when FDA determines an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug, or to minimize the burden on the health care delivery system that is complying with the strategy (section 505-1(g)(2)). In addition, applicant holders may voluntarily submit an assessment of the REMS at any time (section 505-1(g)(1)).

REMS are enforceable under 505-1. FDA may impose civil monetary penalties of up to $250,000 per violation of REMS requirements, not to exceed $1 million in a single proceeding (section 303(f)(4)(A)). Civil monetary penalties may increase if the violation continues more than 30 days after FDA notifies the applicant holder of the violation. The penalties double for the second 30-day period, and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million per proceeding. A drug covered by REMS requirements is also deemed misbranded under section 502(y) if the applicant holder fails to comply with the approved REMS.

The Center for Drug Evaluation and Research (CDER) Office of Scientific Investigations (OSI) takes the lead on enforcement when firms do not comply with REMS requirements.

There are currently no regulations addressing REMS requirements and inspections. If the investigator determines non-compliance with any of the REMS requirements, they should contact their supervisory investigator, the REMS Compliance Team mailbox (CDER-OSI-REMS@fda.hhs.gov), and the REMS Compliance Team CSO POC.

PART II – IMPLEMENTATION

1. Objectives

The objectives of the REMS compliance program are to:

- Assess the firm's compliance with the requirements of section 505-1 of the Act.
- Assess the firm's compliance with the requirements detailed in the REMS approval letter.
- Document the firm's or contractor's implementation of the REMS.
- Verify the accuracy of the REMS assessment information submitted by the firm to the FDA.

2. Program Management Instructions

A. Coverage

The purpose of this compliance program is to provide instructions to field and center personnel for conducting inspections of applicant holders, and contractors working on their behalf, and recommending associated advisory and judicial enforcement actions, as appropriate. Some or all of the required functions of the approved REMS may be contracted to other firms, but the applicant holder retains the statutory obligation to ensure the REMS functions in accordance with the FDA laws related to the approved REMS.

B. Inspection Assignments

The CDER, Office of Compliance (OC), Office of Scientific Investigations (OSI), REMS Compliance Team uses a risk-based approach to select REMS programs for inspection each year. The risk-based approach takes into account factors such as:

- REMS with elements to assure safe use (ETASU);
- REMS with identified issues or violations from a previous REMS inspection;
- REMS with approved modifications since the last inspection;
- REMS that have been identified by the Office of New Drugs (OND) or Office of Surveillance and Epidemiology (OSE) with recognized issues;
- REMS with issues identified during review of the REMS Assessment Report;
- REMS that have never been inspected; and
- REMS not inspected in the last 2-3 years.

1) The REMS Compliance Team issues REMS inspection assignments to the ORA BIMO Inspection POC and through the appropriate information systems. There are no ad hoc, or field-initiated REMS inspections.

   a) The inspection assignment lists the REMS drug product(s), the firm name, inspection goal date, and identifies the REMS Compliance Team CSO POC responsible for the inspection assignment memorandum. The REMS Compliance Team CSO drafts the inspection assignment memorandum containing the specific questions regarding the content of the REMS and sends the memorandum to ORA BIMO Inspection POC prior to the inspection.

   b) The ORA investigator should contact the REMS Compliance Team CSO POC and the REMS Compliance Team mailbox (CDER-OSI-REMS@fda.hhs.gov) at least two weeks prior to the initiation of each inspection to discuss any specific concerns or issues related to the inspection or inspection assignment memorandum.

   c) For inspection assignments that identify a REMS Compliance Team CSO to participate as a Subject Matter Expert (SME) in the REMS inspection, the ORA investigator, as well as the SME, should follow IOM 5.1.2.5 "Team Inspections". The SME should follow established OBIMO procedures to participate in an inspection and obtaining credentials.

   d) The ORA investigator should allot adequate time to complete the REMS inspection as detailed in the inspection assignment instructions, especially in the case when the REMS inspection is conducted in conjunction with a postmarketing adverse drug experience (PADE) inspection.

2) The ORA supervisory investigator should notify the REMS Compliance Team mailbox at CDER-OSI-REMS@fda.hhs.gov of any returned inspection assignment and the reason(s) the assignment was unable to be completed.

C. ORA Investigator Responsibilities

1) Schedule and conduct the REMS inspection (REMS inspections are preannounced).

2) Establish initial contact with the REMS Compliance Team CSO POC identified in the REMS inspection assignment memorandum and the REMS Compliance Team mailbox (CDER-OSI-REMS@fda.hhs.gov) at least two weeks prior to the REMS inspection start date to discuss any specific concerns or issues related to the inspection or inspection assignment memorandum, and for any updates to the assignment.

3) Coordinate inspection timing for inspections that identify a REMS Compliance Team CSO to participate as a Subject Matter Expert (SME) in the REMS inspection.

4) Contact the REMS Compliance Team CSO POC for clarification, if needed, during the REMS inspection.

5) Discuss any potential Form FDA 483 items with supervisory investigator, and consult the CDER REMS Compliance Team at CDER-OSI-REMS@fda.hhs.gov, or the REMS Compliance Team CSO POC listed in the assignment memorandum, as needed, if there are questions or concerns prior to writing and issuing the Form FDA 483.

6) Forward as soon as possible to the REMS Compliance Team CSO POC a copy of any written response to the Form FDA 483 by the inspected party. The ORA investigator should provide the center contact information to the firm so that the response to the Form FDA 483 can be sent directly to the center for review in addition to sending it to the OBIMO correspondence box.

7) All members of the inspectional team, if applicable, will write the EIR.

8) Enter the initial REMS inspection classification into the appropriate information technology system.

D. REMS Compliance Team CSO Responsibilities

1) Consult with other CDER Offices, as needed, to select REMS programs for inspection assignments.

2) Draft and issue the REMS inspection assignment memorandum.

3) Provide expert technical guidance, information, and support to the ORA investigator prior to, during, and after the inspection.

4) Review the EIR and supporting documents to determine final classification of the REMS inspection.

5) The REMS Compliance Team CSO POC will forward to the OBIMO correspondence box for the respective division, a copy of any response to a Form FDA 483 that does not appear to have been shared with the inspecting OBIMO division.

6) Enter the final REMS inspection classification into the appropriate information technology system.

7) Issue post inspection correspondence to the OBIMO Correspondence mailbox for the respective division and the inspected firm.

E. Supervisory CSO Responsibilities

1) Assign the REMS inspection assignment to an investigator.

2) Review and endorse the EIR.

3) Notify the REMS Compliance Team CSO POC of the availability of the completed EIR in the appropriate information technology system.

PART III – INSPECTIONAL

1. Operations

- The REMS program is a statutory program of the Act, and does not have a code of federal regulations (CFR) designation.
- REMS inspections are conducted to determine compliance with section 505-1 of the Act, and the REMS approval letter for the specific drug or biologic product.
- The REMS Compliance Team selects the sites for inspection and issues the inspection assignments to ORA BIMO Inspection POC and in the appropriate information technology system.
- The inspection memorandum addresses specific requirements for the REMS program for the drug. Each inspection memorandum is written to obtain information to determine if the approved REMS is implemented as required by FDA.
- Inspections under this program are domestic and should be preannounced.

A. Inspections

Each REMS is unique, and therefore may have different elements and tools to mitigate the risk(s) of the drug. The inspection assignment will focus on the approved REMS requirements. Listed below are the content areas that a REMS inspection will focus on according to section 505-1(c) of the Act. If additional information or documents need to be collected during an inspection, they will be listed in the assignment memorandum.

1) Medication Guide

The risk evaluation and mitigation strategy for a drug may require that the sponsor develop a Medication Guide, as provided for under 21 CFR 208, that sets forth requirements for patient labeling for human prescription drug products, including biological products. Under 21 CFR 208 and in accordance with section 505-1 of the Act, the firm must ensure that the Medication Guide is available for distribution to patients at the time the patient is dispensed the drug.

If a Medication Guide is an element of the REMS, the ORA investigator should focus on obtaining the following information:

a) A copy of the Medication Guide that is distributed with the drug product specified and verify that is identical to the copy at REMS@FDA, www.fda.gov/rems.

b) Documentation of the mechanisms the firm intends to use, or used, for distribution and dispensing of the Medication Guide.

c) Verify the availability of the Medication Guide to the end user.

d) Any documentation the firm has regarding procedures to identify, report and correct failures to adhere to distribution and dispensing requirements.

e) Documentation of the firm's activities related to the assessment of healthcare provider's and patient's understanding of the messages communicated in the Medication Guide.

2) Communication Plan

The REMS for a drug may require that the sponsor develop and conduct a communication plan targeted to healthcare providers. A communication plan includes tools for disseminating information about the risks addressed by the REMS, including risk messages and messages related to REMS program operations and requirements to assure safe use (505-1(e)(3)).

Examples of REMS tools included in a communication plan are:

- REMS website;
- Dear Healthcare Provider (DHCP) letters, REMS letters, or letters addressed to healthcare providers through professional organizations;
- REMS Factsheets;
- Patient counseling tools for healthcare providers; or
- Journal information piece.

If a communication plan is an element of the REMS, the ORA investigator should focus on obtaining the following information, as outlined in the REMS document:

a) The date of product launch.

b) The source(s) for mailing lists used to distribute letters to the target audience (e.g., physicians (including specialties), pharmacists, professional societies) and verify this information matches what is in the REMS document.

c) The mailing lists used to distribute letters to the target audience (e.g.,

physicians (including specialties), pharmacists, professional societies).

d) The distribution date(s) for the communication plan tools (e.g., Dear Healthcare Provider letter, Dear Professional Society Letter, REMS letter, REMS Factsheet).

e) The method of distribution for the communication plan tools (e.g., email, fax, postal mail, scientific meetings, contract carrier, sales representative detail).

f) The number of undeliverable emails, undeliverable faxes, or returned postal mail for each distribution date of the communication plan.

g) Corrective actions taken to ensure return mailings were reissued.

h) The date journal pieces appeared in each journal or publication, including volume, issue number, and name.

i) The date and name of any scientific meetings attended and list of REMS materials displayed.

j) The date the REMS website went live and verify the website is fully operational.

k) Any documentation or correspondence, including complaints, received by the firm regarding issues with the REMS website.

l) The number of REMS tools (e.g., REMS Factsheets, patient counseling tool kits) distributed by firm's representatives during follow-up details and visits with healthcare providers during the specified time period after approval of the REMS.

m) A copy of all the communication plan tools and verify they are identical to the documents appended to the REMS.

n) Documentation of the firm's activities related to the assessment of targeted REMS stakeholder's (e.g., healthcare provider, patient, pharmacist) understanding of the messages communicated by the REMS program (e.g., knowledge surveys assessing healthcare provider's understanding of risk messages or REMS program requirements).

o) Documentation of the firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

3) Elements To Assure Safe Use (ETASU)

FDA may require that a REMS include such elements as are necessary to assure safe use of the drug. An ETASU will address one or more REMS goals.

a) ETASU A (section 505-1(f)(3)(A))

Healthcare providers who prescribe the drug have particular training or experience, or are specially certified (the opportunity to obtain such training or certification with respect to the drug shall be available to any willing provider in a widely available training or certification method (including an on-line course or via mail) as approved by the Secretary at reasonable cost to the provider).

If the REMS contains ETASU A, the ORA investigator should verify the following information, as outlined in the REMS document:

i. The number of healthcare providers that have received particular training or experience, or are specially certified (i.e., comply with all requirements to become certified – e.g, training, program enrollment, etc.).

ii. The healthcare provider certification process is documented and is in accordance with the approved REMS.

iii. Documentation of the firm's activities related to the implementation of ETASU A (e.g., documentation that healthcare providers receive a notification that they have been certified in the REMS program; maintenance of a validated, secure database of healthcare providers who are certified).

iv. The firm identifies and addresses healthcare provider non-compliance.

v. Documentation of the firm's activities related to the assessment of targeted healthcare provider's understanding of the messages communicated by the REMS program (e.g., knowledge surveys assessing healthcare provider's understanding of risk messages and/or REMS program requirements).

vi. Documentation of the firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

b) ETASU B (section 505-1(f)(3)(B))

Pharmacies, practitioners, or other health care settings that dispense the drug are specially certified (the opportunity to obtain such certification shall be available to any willing provider).

If the REMS contains ETASU B, the ORA investigator should verify the following information, as outlined in the REMS document:

i. The number of pharmacies, practitioners, or other health care settings that dispense the drug that are specially certified (i.e., comply with all requirements to become certified – e.g., training, program enrollment, etc.).

ii. Pharmacy, practitioner, or other health care setting's certification process is documented and is in accordance with the approved REMS.

iii. Documentation of the firm's activities related to the implementation of ETASU B (e.g., documentation that pharmacies, practitioners, or other healthcare settings that dispense the drug receive a notification that they have been certified in the REMS program; maintenance of a validated, secure database of certified pharmacies, practitioners, or health care settings).

iv. The firm identifies and addresses pharmacy, practitioner, or health care setting non-compliance.

v. Documentation of the firm's activities related to the assessment of targeted stakeholder's understanding of the messages communicated by the REMS program and compliance with program requirements (e.g., knowledge surveys assessing pharmacist, healthcare provider, or clinical setting designee's understanding of risk messages and/or REMS program requirements; site audits).

vi. Documentation of the firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

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

The drug is dispensed to the patient only in certain health care settings, such as hospitals.

If the REMS contains ETASU C, the ORA investigator should verify the following information, as outlined in the REMS document:

i. The drug is shipped only to certified facilities and these facilities are the type of facility specified in the REMS document (e.g., hospitals and facilities that have met certain conditions or have certain capabilities; physician's office equipped to treat potential risks following administration of the drug).

ii. Healthcare setting or wholesaler/distributor enrollment process is documented and is in accordance with the approved REMS.

iii. The firm identifies and addresses health care setting or product wholesaler and distributor non-compliance.

iv. Documentation of the firm's activities related to the assessment of targeted stakeholder's compliance with REMS program requirements (e.g., site audits).

v. Documentation of the firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

d) ETASU D (section 505-1(f)(3)(D))

The drug is dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results.

If the REMS contains ETASU D, the ORA investigator should verify the following information, as outlined in the REMS document:

i. The drug is dispensed to patients with prior evidence or other documentation of safe use conditions as described in the approved REMS (e.g., patients have been counseled about the risks and benefits of the product and have signed an acknowledgement that they understand the risks and benefits of the product; patients have been provided a copy of patient educational materials and demonstrated that they understand the risks and benefits of the product; patients receive drug only after specified authorization (e.g., checking laboratory values, or checking for physician qualifications (stickers) on the

prescription) is obtained and verified by the pharmacy).

ii. The firm identifies and addresses pharmacy, practitioner, patient, or health care setting non-compliance.

iii. Documentation of the firm's activities related to the implementation of ETASU D (e.g., documentation that certified prescribers are able to submit completed forms documenting safe use conditions as specified; documentation that certified pharmacies or health care facilities can verify documentation of safe use conditions; maintenance of a validated, secure database; maintenance of a REMS Program Call Center).

iv. Documentation of the firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

e) ETASU E (section 505-1(f)(3)(E))

Each patient using the drug is subject to certain monitoring.

If the REMS contains ETASU E, the ORA investigator should verify the following information, as outlined in the REMS document:

i. Each patient receives the monitoring specified in the approved REMS (e.g., patient's laboratory tests are monitored on a specified basis to prevent the serious risk; patients are required to contact the prescriber within a specified period of time after beginning treatment with the drug to ensure they are still appropriate candidates for treatment; patients are required to contact their prescriber periodically during and following treatment to ensure they did not experience the serious risk associated with use of the drug).

ii. The firm identifies and addresses pharmacy, practitioner, patient, or health care setting non-compliance.

iii. Documentation of the firm's activities related to the implementation of ETASU E (e.g., documentation that the required monitoring takes place according to schedule; availability of materials required for monitoring (e.g., checklist)).

iv. The firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended

materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

f) ETASU F (section 505-1(f)(3)(F))

Each patient using the drug is enrolled in a registry.

There are two types of registries associated with a REMS: (1) Mandatory REMS Registry and (2) Voluntary REMS Registry.

A Mandatory REMS Registry may be established with the primary purpose of ensuring safe use of the drug – drug access is contingent on patient enrollment. Information that may be collected on enrolled patients includes:

- information on clinical outcomes,
- clinical and laboratory data,
- safety information,
- data on compliance with prescribed management and prescribing protocols, and
- data on the impact of tools for ensuring compliance and outcomes.

A Voluntary REMS Registry may be required under a REMS with the objective of collecting long-term safety information; however, participation in the registry cannot be required for patients to receive drug therapy.

If the REMS contains ETASU F, the ORA investigator should verify the following information, as outlined in the REMS document:

i. Patients are enrolled in a registry.

ii. The firm identifies and addresses patient registry enrollment non-compliance.

iii. Documentation of the firm's activities related to the implementation of ETASU F (e.g., maintenance of a validated, secure database of enrolled patients).

iv. The firm's activities related to surveillance of the risks addressed by the REMS program as described in the REMS, REMS appended

materials, and REMS approval letter (e.g., drug utilization information, postmarketing case reports).

4) Implementation System

The REMS may include a system through which the firm is able 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.

If an Implementation System is an element of the REMS, the ORA investigator should verify the following information, as outlined in the REMS document:

a) All processes and procedures are in place and functioning to support the requirements of the REMS.

b) Documentation of distribution and dispensing, certified prescriber, certified pharmacy, and enrolled patient records to meet REMS requirements.

c) Documentation and maintenance of a validated, secure database of all certified stakeholders in the REMS program.

d) Documentation and maintenance of a REMS Program Call Center and a REMS program website.

e) The firm conducts audits and maintains an ongoing audit plan.

f) The firm takes reasonable steps to improve implementation of and compliance with the requirements in the REMS program based on monitoring and evaluation of the REMS program.

5) REMS inspections may be conducted at the contractors of the firm. FDA may inspect facilities (contractors) that perform some or all of the requirements of the REMS on behalf of the responsible person. During an inspection of a contractor, the ORA investigator should verify that the contractor has implemented all requirements of the REMS program as contracted. The following information is reviewed or collected during an inspection of a contractor:

a) A copy of the contract between the sponsor and the contractor (financial information may be omitted).

b) A list of the firm(s) employed by the contractor, and the names and titles

of those who ensure the duties listed in the REMS program contract are performed.

c) A description of the processes or functions performed by the contractor for the REMS program.

d) Records pertaining to the REMS that are held by the contractor.

e) Any available REMS training records or standard operating procedures.

B. Sample Collections

There are no sample collections planned under this program.

2. Reporting

A. FORM FDA 483, Inspectional Observations

Document observed deviations from the approved REMS on the Form FDA 483, "Inspectional Observations". See Part V, Table 1 for a list of possible REMS citations.

If there are questions or concerns prior to documenting any observations on a Form FDA 483, contact the supervisory investigator, and consult the CDER REMS Compliance Team at CDER-OSI-REMS@fda.hhs.gov, or the REMS Compliance Team CSO POC listed in the assignment memorandum.

B. Establishment Inspection Report (EIR)

The ORA investigator should refer to the Investigations Operations Manual (IOM), subchapters 5.5.7 "ADVERSE EVENT REPORTING/Risk Evaluation and Mitigation Strategies (REMS)" and subchapter 5.10 "REPORTING" for guidance on reporting inspectional findings.

The REMS EIR requires detailed narratives for every subsection listed below.

Required elements:

- Summary
- Administrative data
- History
- Interstate Commerce

- Identify and document interstate commerce of the REMS product or components of the REMS product

- Individual Responsibility and Persons Interviewed
- Medication Guide (if applicable)
- Communication Plan (if applicable)
- ETASUs (if applicable)
- Implementation System (if applicable)
- Objectionable Conditions and Management's Response
- General Discussion with Management
- Exhibits Collected
- Attachments

1) To support a regulatory or administrative action, the information contained in the EIR may be used. The EIR and exhibits must clearly document all findings that could significantly influence the decision-making process and include sufficient information to support the recommended classification.

2) The endorsement to the EIR should provide a summary of the major observations noted during the inspection.

C. Post-Inspection Communications

The Office of Bioresearch Monitoring Operations (OBIMO) division should notify the REMS Compliance Team mailbox (CDER-OSI-REMS@fda.hhs.gov) and the REMS Compliance Team CSO POC of any post-inspection communications with the inspected person.

PART IV – ANALYTICAL

There are no analytical activities planned under this program.

PART V – REGULATORY/ADMINISTRATIVE STRATEGIES

The following guidance is to be used in conjunction with the instructions in FMD-86[18] for initial OBIMO division and center classification of EIRs generated under this Compliance Program:

No Action Indicated (NAI) - No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action);

Voluntary Action Indicated (VAI) - Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action; and

Official Action Indicated (OAI) - Regulatory and/or administrative actions will be recommended.

Once an OAI decision is reached, additional information (e.g., previous inspectional findings, correspondence, or other information) may assist the center in determining which type of post-inspection correspondence is appropriate.

Inspectional findings documenting that a firm is not following the approved REMS may be used as evidence for taking regulatory or judicial actions. The center may rely on information from inspections of contractors that assumed some or all of the firm's REMS responsibilities to determine the firm's compliance with the REMS. The CDER REMS Compliance Team and OSI management will be responsible for drafting, developing, and issuing all Untitled and Warning Letters. The REMS Compliance Team will be responsible for the final classification of inspections. The OBIMO division should consult with the REMS Compliance Team when a regulatory action recommendation is considered to allow for discussion of the recommendation.

A. Warning Letters

The issuance of a Warning Letter (WL) may be warranted when the inspection uncovers significant objectionable conditions related to compliance with the REMS. The CDER REMS Compliance Team and OSI management will evaluate all WL recommendations on a case-by-case basis.

B. Untitled Letters

An Untitled Letter (UL) may be warranted when the deficiencies found at the firm are severe enough to justify a formal letter to the firm, but do not meet the threshold of regulatory significance for a WL.

Factors that influence the issuance of a WL or UL include the nature and extent of the violations (e.g., repeat or deliberate), the compliance history of the inspected firm, and the corrective actions implemented by the firm.

If the center chooses to issue a WL and allow the firm to submit a detailed corrective action plan or

alternate approach that is acceptable to FDA, the center should nevertheless be prepared to initiate necessary enforcement actions should the firm not respond appropriately (i.e., fails to respond, fails to develop an adequate corrective action plan, or is found during a subsequent inspection to have failed to comply with a corrective action plan).

Generally, FDA can take the following enforcement actions for failure to comply with REMS requirements if the firm does not implement adequate corrective actions and continues to violate the REMS following the issuance of a WL or UL:

- Seizure of the drug subject to the REMS;
- Injunction; or
- Civil monetary penalties.

The following table lists possible REMS observations and citations. Contact your supervisory investigator, and consult the REMS Compliance Team CSO POC listed in the assignment memorandum, if there are questions or concerns prior to documenting any observations on a Form FDA 483.

Table 1 – REMS Observations/Citations

• Failure to comply with REMS Medication Guide - FDCA Section 505-1[355-1](e)(2)(a)
• Failure to comply with REMS Communication Plan - FDCA Section 505-1[355-1](e)(3)
• Failure to comply with REMS Elements to Assure Safe Use (ETASU) A - FDCA Section 505-1[355-1](f)(3)(A)
• Failure to comply with REMS Elements to Assure Safe Use (ETASU) B - FDCA Section 505-1[355-1](f)(3)(B)
• Failure to comply with REMS Elements to Assure Safe Use (ETASU) C - FDCA Section 505-1[355-1](f)(3)(C)
• Failure to comply with REMS Elements to Assure Safe Use (ETASU) D - FDCA Section 505-1[355-1](f)(3)(D)
• Failure to comply with REMS Elements to Assure Safe Use (ETASU) E - FDCA Section 505-1[355-1](f)(3)(E)
• Failure to comply with REMS Elements to Assure Safe Use (ETASU) F - FDCA Section 505-1[355-1](f)(3)(F)
• Failure to comply with REMS Implementation System - FDCA Section 505-1[355-1](f)(4)
• Failure to comply with REMS Timetable for Submission of Assessments - FDCA Section 505-1[355-1](d)

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. References

   A. The list of FDA approved risk evaluation and mitigation strategies (REMS): https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

   B. Guidance for Industry – Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications (DRAFT Sept 2009) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

   C. Guidance – Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) (Nov 2011) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf

   D. 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

   E. REPORT: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS) (Sept 2014) http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf

2. Program Contacts

   A. REMS

   For questions about REMS and compliance program issues:

   Risk Evaluation and Mitigation Strategies (REMS) Compliance Team
   Office of Scientific Investigations
   Office of Compliance, CDER
   Food and Drug Administration
   10903 New Hampshire Avenue
   WO 51, Room 5359
   Silver Spring, Maryland 20993-0002

   REMS Compliance Team CSO POC (identified in the inspection assignment)

   CDER-OSI-REMS@fda.hhs.gov

B. Operational

For operational questions:

Office of Regulatory Affairs (ORA)
Office of Medical Products and Tobacco Operations (OMPTO)
Office of Bioresearch Monitoring Operations (OBIMO)
ORA BIMO Inspection POC

PART VII - CENTER RESPONSIBILITIES

1. Centers

   A. Assess compliance issues related to possible deviations and violations of the specific drug REMS requirements;

   B. Identify, prepare, issue, and monitor all inspection assignments;

   C. Communicate specific REMS concerns, if any, to investigator prior to inspection;

   D. Serve as the POC for field inquiries on REMS assignments and compliance issues;

   E. Provide guidance and support to the field during all phases of inspections, investigations, and regulatory actions;

   F. Review and evaluate EIRs and regulatory recommendations from OBIMO divisions;

   G. Submit approved regulatory recommendations to the Office of Chief Counsel, if required;

   H. Review and determine final classification of EIRs, and enter the classification into the appropriate information technology system;

   I. Issue post-inspection correspondence to the inspected firm;

   J. Act as the liaison between OBIMO and other center offices for the review and evaluation of REMS inspection findings;

   K. Notify other center offices, as appropriate, of significant REMS violations; and

   L. Attend inspections as a SME, if needed.

   M. Write portions of the EIR as appropriate.

2. OBIMO Office of Regulatory Affairs (ORA)

   A. ORA OBIMO HQ receives all REMS inspection assignment memorandums from the center via the ORA BIMO Inspection POC email. OBIMO assigns to the appropriate division (OBIMO East (Division 1) or OBIMO West (Division 2)).

   B. OBIMO division management assigns the inspection to an ORA investigator.