SOPP 8417: Implementation and Management of Risk Evaluation and Mitigation Strategies (REMS)

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff for implementing and maintaining Risk Evaluation and Mitigation Strategies (REMS).

II. Scope

A. This SOPP applies to:

1. An initial REMS as part of an original Biologics License Application (BLA) or New Drug Application (NDA), or a new REMS being needed as part of an efficacy supplement;

2. Management and review of REMS revisions and minor/major modifications to an approved REMS;

3. Management and review of incoming REMS assessments for an approved REMS;

4. Management and review of incoming assessment instruments and methodology for an approved REMS; and,

5. Management of a new REMS for an approved product based upon New Safety Information (NSI).

III. Background

A. Section 505-1 of the Federal Food, Drug and Cosmetic (FD&C) Act, as added by FDAAA and later amended by FDASIA, authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of the drug (drug/biologic) outweigh its risks.

1. FDA can require an applicant to submit a proposed REMS when the office responsible for reviewing the drug (i.e., a CBER product office) and the office responsible for post-approval safety with respect to the drug [i.e., CBER/Office of Biostatistics and Pharmacovigilance (OBPV)] determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. In making such a determination, the following factors must be considered:

   a. The estimated size of the population likely to use the drug.

   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 the disease or condition to be treated.

   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.

      i. For CBER products, this assessment may also represent whether a product is a new technological advancement.

B. A REMS can include one or more of the following elements to ensure that the benefits of a drug outweigh its risks: a Medication Guide, Communication Plan, an Elements to Assure Safe Use (ETASU), and an Implementation System.

1. One or more ETASUs may be required if the drug has been shown to be effective but is associated with a specific serious risk.

a. If a REMS includes certain ETASUs, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the elements (e.g., development of a REMS specific Web site or call center to facilitate enrollment; establishment of electronic databases of certified health care settings). See Section 505-1(f)(4) of the FD&C Act.

C. A required REMS must be operational before a new drug is introduced into interstate commerce or if a new indication approval requires the need for a REMS.

1. Specific requirements of approved REMS are described in detail in the applicant's REMS document and within REMS materials publicly available on the FDA's REMS@FDA website.

2. General metrics for all of FDA's REMS can be found on the REMS Public Dashboard.

D. FDASIA amended sections 505-1(g) and (h) of the FD&C Act to give FDA the authority to require a REMS modification when necessary to:

1. Ensure the benefits of the drug outweigh its risks.

a. FDASIA also requires FDA to review and act on REMS modifications to conform to approved safety labeling changes, or to safety labeling changes that FDA has directed the applicant to make.

2. Minimize the burden on the health care delivery system to comply with the REMS.

Additionally, an applicant can propose a modification to an approved REMS at any time, accompanied by an adequate rationale to support the change. The *Guidance for Industry*: *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* describes which changes can be implemented and identifies what types of changes constitute REMS revisions or minor and major REMS modifications, as well as the time frames in which FDA must review and act on each type of modification.

E. Approved REMS must be assessed at specific intervals to determine if the REMS program is meeting its goals and whether modifications are warranted to further mitigate risks. Although the timetables for assessing REMS vary from case to case, minimum timepoints are at 18 months, three years, and seven years from REMS approval. An applicant must submit a REMS Assessment when they submit a supplemental application for a new indication. An applicant may also submit an assessment at any time.

IV. Definitions

A. **Risk Evaluation and Mitigation Strategy (REMS) -** A required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks.

B. **Medication Guide (MG) -** A paper handout distributed with some prescription medicines which addresses issues specific to particular drugs and drug classes and contains FDA-approved information that can help patients avoid serious adverse events. Medication Guides can be required when FDA determines that certain information is necessary to prevent serious adverse effects, patient decision-making should be informed by information about a known serious side effect, or patient adherence to directions for the use are essential to its effectiveness.

C. **Communication Plan (CP) -** A component of a REMS targeted to healthcare providers to support implementation of the REMS. A Communication Plan can include sending letters to healthcare providers; disseminating information about REMS elements to encourage implementation by healthcare providers or to explain certain safety protocols, such as medical monitoring by periodic laboratory tests; or disseminating information to healthcare providers through professional societies about any serious risks of the drug and any protocol to assure safe use.

D. **Elements To Assure Safe Use (ETASU) -** For certain REMS, these are required clinical or administrative activities that can include:

- Education and certification of healthcare providers
- Education and certification of those who dispense the product
- Restricting product use only to specified healthcare settings
- Documentation of safe-use condition
- Patient monitoring
- A patient registry

E. **ETASU REMS -** A REMS program that contains an ETASU.

F. **REMS Document/Document Template -** An applicant- written document, utilizing an FDA created template, that establishes the goals and requirements of the REMS as they relate to the required REMS elements. Note: The FDA *Guidance for Industry: Format and Content of a REMS Document* provides applicants recommendations on drafting a proposed REMS document using a standardized format.

G. **REMS Materials -** All proposed materials (not including the REMS Document or REMS Supporting Document) that are included and approved as part of a REMS (e.g., communication and educational materials, enrollment forms, prescriber, and patient agreements).

H. **REMS Supporting Document -** An applicant-written document which expands on information in the REMS document, and provides additional information about the REMS, such as the rationale for and supporting information about the design, implementation, and assessment of the REMS. Note: The REMS supporting document is not available on FDA's website for public viewing.

I. **REMS Review Memorandum -** A standalone CBER review memo generated by the responsible product review office when the need for a new REMS has been formally determined.

J. **REMS Modification Review Memorandum -** A standalone CBER review memo generated by the responsible product review office when the need for a major REMS modification has been formally determined and the modification impacts one (or more) of the of following: 1) Modifying the Goal, 2) Adding one or more elements to the REMS [i.e., medication guide (MG), Communication Plan (CP), Elements to Assure Safe Use (ETASU)] or, 3) removing one, or more (i.e., MG, CP, ETASU)elements, or eliminating the entire REMS.

K. **REMS Assessment -** At periodic intervals following REMS approval according to the required timetable, applicants must submit a REMS assessment. The Assessment Plan is described in the approval letter and the applicant provides an assessment report to FDA that includes analysis, findings and conclusions related to whether the REMS is meeting its goals and what if any, modification might be needed.

L. **REMS Meeting -** A scheduled internal CBER meeting between the responsible product review office and OBPV, along with other relevant regulatory staff, to discuss major safety findings and the risk/benefit profile of the product in the context of a proposed or modified REMS. Refer to *R 910.02: Attendee Table for BLA/NDA Meetings* for who to invite to this meeting.

M. **REMS Notification Letter -** A letter formally notifying the applicant of the need for a REMS in the post-approval setting.

N. **REMS Modification Notification Letter** - A letter formally notifying the applicant of the need for a REMS modification in the post-approval setting.

O. **New Safety Information (NSI)** - As defined in section 505-1(b)(3) of the FD&C Act, new safety information includes information derived from a clinical trial, an adverse event report, a post-approval study, or peer-reviewed biomedical literature, data derived from the postmarketing risk identification and analysis system under section 505(k), or other scientific data deemed appropriate about (1) a serious risk or unexpected serious risk associated with use of a drug since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug, or (2) the effectiveness of the approved risk

evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

P. Attestations - Statements on enrollment forms and other REMS materials that detail the REMS requirements a stakeholder is responsible for under the REMS and must agree to perform to participate in the REMS.

V. Policy

A. The responsible product office and OBPV, Division of Pharmacovigilance (DPV), are to work together to determine when a REMS is required or if REMS modifications are needed.

B. CBER will generally consult the Center for Drug Evaluation and Research (CDER)'s Office of Safety and Epidemiology (OSE), Division of Risk Management (DRM) for a new REMS to ensure cross-Center interpretation and implementation of REMS requirements. OBPV will determine whether a consult is needed for major REMS modifications or assessments. For information on inter-center consults refer to *SOPP 8001.5: Inter-Center Consultative Review Process*

C. The CBER Safety-Related Working Group (CBER SWG) will provide Center level oversight and concurrence with all needed REMS provisions.

D. The Office of Chief Counsel (OCC) will be notified and provide clearance of all new proposed REMS that have an ETASU (i.e., ETASU REMS) and provide clearance of major ETASU REMS modifications (including elimination of a REMS) when there are changes to the REMS Document and/or need to draft a REMS Modification Review Memorandum(see section IV, Definitions, J.).

E. The signatory authority on REMS letters is an individual "at or above the level of individuals empowered to approve a drug" (section 505-1(a)(4) of the Act). Refer to Staff Manual guides for Delegations of Authority.

F. CBER will not approve an original application or efficacy supplement without a REMS once it has been determined that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

G. The REMS Review Memorandum must be included as part of the administrative file when a new REMS is determined to be needed. The REMS Modification Review Memorandum must be included as part of the administrative file for certain major REMS modifications as noted in the definition above.

1. Although these memorandums might recapitulate aspects of the primary review memos written by the responsible product office clinical reviewer and/or the OBPV epidemiologic reviewer, the memorandums will be a

separate document to facilitate clearance and will be written by the responsible product office.

H. If the applicant noted any serious safety issue(s) that emerged during product development or during foreign marketing experience prior to U.S. approval, the pre-new drug application (pre-NDA)/pre-biologics license application (pre-BLA) or pre-new drug supplemental application (pre-sNDA)/pre-biologics license supplemental application (pre-sBLA) meeting should include a preliminary discussion of the potential need for a REMS. Based upon this preliminary discussion, if CBER believes a REMS may be required as a condition of approval a proposed REMS (which includes a REMS Document, REMS Materials, and REMS Supporting Document) should be submitted with the initial submission.

I. In the pre-approval setting, if a REMS is determined necessary, but has not been submitted to the marketing (original or efficacy) application, CBER will notify the applicant as soon as possible via standard communication practices (telecon, secure email, etc.) that a REMS is required, generally within 4 weeks (priority review) or 6 weeks (standard review) following the Mid-Cycle Meeting.

J. In the post-approval setting (unrelated to an efficacy supplement), CBER will notify the applicant as soon as possible with a formal REMS Notification Letter if FDA CBER becomes aware of NSI after a drug is approved and determines a REMS is necessary **OR** if the applicant submits a proposed REMS (post-approval) and CBER determines that different elements are needed.

K. For all original REMS approvals, the REMS document (not the REMS supporting document) and all REMS materials are enclosed with the approval letter.

L. In the post-approval setting, CBER will notify the applicant with a formal REMS Modification Notification Letter if a modification is determined to be needed.

M. CBER will communicate REMS issues in the Complete Response (CR) letter if:

1. An applicant was notified that a REMS is required, but did not submit a proposed REMS for review by the target action date;

2. The applicant submitted a required REMS for review late in the review cycle and could not be reviewed by the target action date.

3. The applicant submitted a required REMS for review, but it was determined to be inadequate and acceptable elements could not be agreed upon before the target action date.

N. Revisions, and Minor or Major REMS Modifications:

1. Changes to approved REMS will be categorized by the degree of the potential effect on the risk message (the information provided in the REMS about the

serious risks or safe use of the drug) and/or the REMS requirements as described in the *FDA Guidance for Industry: Risk Evaluation and Mitigation Strategies: Modifications and Revisions*. Refer to the guidance for specific examples of each type of categorical change.

a. Revisions are editorial changes that do not affect the information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug.

i. Revisions are submitted as product correspondence and can be implemented immediately following receipt of the submission by the FDA.

b. REMS modifications are divided into two categories:

i. Minor modifications have a limited effect on the information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug and the actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or on the REMS materials that support those actions.

a) Minor modifications will be submitted as a CBE-30 supplement and reviewed and acted on no later than 60 days from receipt. The applicant can implement the proposed modifications 30 days after FDA receipt; however, the modifications are not considered final until approved.

ii. Major modifications have a substantial effect on the information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug and the actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or on the REMS materials that support those actions.

a) Major modifications will be submitted as a Prior Approval Supplement (PAS) and the applicant cannot implement the proposed modifications until approved.

b) Major modifications made as part of an efficacy supplement will be reviewed and acted upon as per the determined PDUFA or target action date.

c) Major modifications submitted which are not due to safety labeling changes will be reviewed and acted upon no later than 180 days from receipt.

d) Modifications due to safety labeling changes including those the application holder initiates under current regulations (CBE-0

supplement) and those labeling changes the FDA requires under 505(o)(4) will be submitted as prior approval supplements, either as:

A conforming REMS modification (transferring new label language into the existing REMS or REMS materials) which will be reviewed and acted upon no later than 60 days from receipt of the proposed modification; or,

A non-conforming REMS modification (changes made to overall design, programmatic changes, and/or implementation changes) which will be reviewed and acted upon no later than 180 days from receipt of the proposed modification.

2. The determination for CBER requiring a modification will be based upon the threshold to 1) ensure the benefits continue to outweigh the risks or 2) to minimize burden on the healthcare system complying with the REMS. CBER will specify the change and type of submission (CBE-30 or PAS) along with the rationale for the needed modification to the applicant.

3. All submitted proposed major or minor modifications should include an updated REMS Supporting Document, if applicable, to align with the proposed changes to the REMS program.

4. If a proposed REMS modification is submitted as part of an efficacy supplement for a new indication of use, the applicant will submit a REMS assessment that is required in accordance with section 1(g)(2)(A) of the FD&C Act to support the proposed REMS modification.

5. For all modification approvals, the revised REMS document (not the REMS supporting document) and all REMS materials are enclosed with the approval letter.

6. Submissions that contain REMS changes of different types will be reviewed and acted on based on the time frame for the longer review clock. CBER will review and act on submissions that include both minor and major REMS modifications within 180 days of receipt. CBER will review and act on submissions containing both minor modifications and REMS revisions within 60 days.

7. CBER intends to post updated REMS revisions on the FDA REMS website within 14 days of receipt of the submission and within 3 days of approval for any REMS modifications. **Note: All REMS materials associated with the REMS must be re-posted, even if a particular REMS material did not have changes.**

8. For a REMS elimination, OBPV and the relevant Product Office will prepare and issue a Safety Communication at the time of the approval of the PAS.

O. Received REMS assessments will generally be reviewed within 6 months of receipt.

1. If the applicant submits a proposed REMS modification in the same submission with a REMS assessment:

   a. CBER will require the submission to be unbundled into two submissions for administrative purposes (i.e. different review clocks) if the modification is minor (CBE-30).

   b. For a major REMS modification (PAS) submitted by the applicant with an assessment, CBER may choose to review the REMS modification in conjunction with a required REMS assessment for administrative purposes (i.e., similar review clocks); however, the proposed REMS modification cannot be implemented by the applicant until approved.

P. The applicant is responsible for developing and updating any necessary REMS assessment instruments or methodology. The applicant should submit the methodology for review at least 90 days before the proposed assessment/surveys will be conducted. CBER will provide feedback and comments on REMS methodological approaches and study protocols used to assess a REMS program for products within 90 days of receipt.

1. If CBER finds minor-moderate revisions are needed, the applicant will be instructed to submit the revised protocol/methodology when they submit the next REMS assessment with the survey results.

2. If CBER finds extensive revisions are needed, the applicant should not implement the REMS assessment instruments or methodology and instead resubmit the revisions as soon as possible for CBER re-review.

3. When any CBER comments/requested changes have been addressed, the applicant must update the REMS Supporting Document as applicable (which includes specific assessment instrument and methodology information).

Q. REMS components may be complex and an incoming submission to a pending application or supplement may be classified as a major amendment and extend the PDUFA clock, if applicable and deemed necessary, by the responsible review office. Generally, changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.

VI. Responsibilities

A. Pharmacovigilance Reviewer (OBPV)

1. Identifies the potential need for a REMS;
2. Participates in discussions on the need for a REMS;
3. Completes primary reviews for original REMS, REMS modifications, and REMS assessments, and any REMS Assessment Instruments and Methodology.
4. Request a CDER DRM consult when needed.
5. Present at SWG meetings as needed.

B. Clinical Reviewer (product office)

1. Identifies the potential need for a REMS;
2. Participates in discussions on the need for a REMS;
3. Documents the need for a REMS in their primary review, completes the REMS Memo or REMS Modification Memo as needed.
4. Present at SWG meetings as needed.

C. Product Office Regulatory Project Manager (RPM) (Product Office RPM)

1. Ensures REMS meetings are scheduled, as necessary;
2. Participates in discussions on the need for a REMS;
3. Ensures all REMS related documents are completed, revised, and entered in RMS-BLA through CBER Connect, excluding documents authored by OBPV staff;
4. Ensures all approved REMS materials and the REMS Document are submitted to OCOD (use email: CBER-OCOD-Action Packages) for a disclosure review and posted to FDA's REMS webpage;
5. Serves as lead point of contact for discussing REMS with the applicant.
6. Closes out minor REMS revisions with a Product Correspondence final review memo.
7. Requests and submits any needed CDER/DRM consults.

D. OBPV RPM

1. Facilitates OBPV Reviewer assignments OBPV

E. CBER SWG Representative in Relevant Product Office and OBPV

1. Facilitates communication between the review team and the CBER SWG;

2. Serves as an office resource on questions related to FDAAA safety provisions, including REMS, when needed.

F. CBER SWG

1. Interprets the policies and procedures used by all CBER Offices pertinent to patient-related safety issues. This committee is overseen by the Associate Director for Policy and the Associate Director for Review Management.

2. Provides Center-level concurrence for all proposed new proposed REMS, major REMS modifications, and REMS assessments (as needed).

G. CBER SWG Executive Secretary

1. Manages the CBER SWG Meeting and is the point of contact for discussing regulatory issues and clearance of REMS related submissions.

H. Clinical and Pharmacovigilance Supervisors

1. Participates in discussions on the need for a REMS;

2. Reviews the REMS Memo, and letters;

3. Signs REMS Memo (clinical supervisor only).

I. Director, Division of Pharmacovigilance

1. Participates in the discussion on the need for a REMS;

2. Reviews the REMS Memo, REMS Notification Letter, and approval or CR Letter.

J. Division Director or designee in Relevant Product Office

1. Participates in the discussion on the need for a REMS;

2. Reviews the, REMS Memo, REMS Notification Letter, and approval or CR Letter;

3. Signs the REMS Memo.

K. Office Director in OBPV

1. Participates in discussions on the need for a REMS;

2. Reviews the REMS Memo, REMS Notification Letter, and approval or CR Letter.

L. Office Director or designee in Relevant Product Office

1. Participates in discussions on the need for a REMS;

2. Reviews the REMS Memo, and REMS Notification Letter;

3. Signs the REMS Memo, REMS Notification Letter, and approval or CR Letter.

M. FDA Office of Chief Counsel (OCC)

1. For new ETASU REMS, provides clearance of draft REMS Memo, draft REMS document, any attestations (e.g., pharmacies and/or hospitals attesting to specific experience or knowledge, before enrollment into a REMS program).

2. For major modifications to an existing ETASU REMS, provides clearance of draft REMS Modification Memo if needed, (see section IV, Definitions, J.), revised REMS document (if needed), and if needed, any attestations (e.g., pharmacies and/or hospitals attesting to specific experience or knowledge, before enrollment into a REMS program).

   Note: OCC does not need to review draft approval letters for new REMS or major modifications to ETASU REMS unless there is significant deviation from letter template language.

N. Office of Communication, Outreach and Development/Division of Disclosure and Oversight Management/Electronic Disclosure Branch (OCOD/DDOM/EDB)

1. Performs a disclosure review of the approved REMS document (not the REMS supporting document) and **all** REMS materials and coordinates posting to FDA's REMS website.

VII. Procedures

A. Initial REMS for an Original Application or a New REMS as part of an Efficacy Supplement

1. Discuss the need for a possible REMS as a condition for approval as soon as the filing meeting. If the application is to be filed, and a REMS may be required, request that the Product Office RPM schedule an internal REMS meeting with OBPV two weeks prior to the mid-cycle meeting. **[Pharmacovigilance Reviewer]**

2. Consult CDER/OSE/DRM and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

a. Send the request for consult via the Inter-Center Consult Request (ICCR) process (see SOPP 8001.5). **[Product Office RPM]**

3. Schedule the REMS meeting. Consult R 910.02: Attendee Table for BLA/NDA Meetings on who from the review team to invite. **[Product Office RPM]**

4. Facilitate the REMS meeting. The Product Office and OBPV should be prepared to discuss the major safety findings and the risk/benefit profile of the product in context of a proposed REMS. A goal is to reach preliminary consensus at the REMS meeting prior to presenting at a CBER SWG meeting. **[Product Office RPM]**

5. Present the potential need for a REMS at a CBER SWG meeting within three weeks following the mid-cycle meeting:

a. Notify the Executive Secretary of the CBER SWG for scheduling. **[Office SWG Representative]**

b. One week prior to the scheduled meeting, send the REMS background materials, which will provide an overview of the product, safety risk that the REMS will mitigate, and proposed REMS elements to the CBER SWG Executive Secretary. **[Clinical and Pharmacovigilance Reviewers]**

The CBER SWG meeting provides decisional concurrence at the Center level on the need for a REMS.

6. Within four weeks (priority review) or six weeks (standard review) following the mid-cycle meeting, notify the applicant via standard communication practices (telecon, secure email) on the REMS determination. The applicant must be informed if the proposed REMS was included in the original/ supplemental submission or if a REMS is determined to be required based on outcome of the SWG discussion. In the communication, provide the weblink to the REMS guidance materials and the REMS template. Note: A formal REMS notification letter should be sent in lieu of other communication practices in any instances as per Section V. Policy. **[Product Office RPM]**

7. Complete the primary review no later than two months prior to the PDUFA or the target action date. Send any comments regarding needed changes to the REMS document and supporting document to the Product Office RPM to communicate to the applicant. **[Clinical Reviewer and Pharmacovigilance Reviewer]**

8. Begin drafting the REMS Review Memorandum no later than two months prior to the PDUFA or target action date. **[Clinical Reviewer]**

9. If the REMS contains an ETASU, send the final draft REMS document and any attestations, if applicable, to CDER/OSE/DRM for review at least five weeks prior to the PDUFA or target action date. **[Product Office RPM]**

    a. After notification from the Product Office RPM of CDER/OSE/DRM review and acceptance, send the above materials and the REMS Review Memorandum to OCC for clearance at least four weeks prior to the PDUFA or target action date. **[SWG Executive Secretary]**

10. Provide the final OCC cleared REMS document and any FDA revised REMS materials to the applicant for review at least one week prior to the PDUFA or target action date. **[Product Office RPM]**

11. Finalize the REMS Review Memorandum and obtain final concurrence. **[Clinical Reviewer]**

12. Draft, circulate, and obtain final concurrence of the CR or approval letter containing REMS template language, as appropriate. **[Product Office RPM]**

13. Communicate the CR or approval letter to the applicant no later than the PDUFA or target action date. If an approval action, submit REMS materials and the REMS document (not the REMS Supporting Document) along with the Transmittal memo, approval letter, SBRA, and Package Insert to OCOD for a disclosure review (use email: CBER-OCOD-Action Packages). OCOD will submit the material for posting to FDA REMS. Note: REMS materials are to be posted within three days of the approval date. **[Product Office RPM]**

B. Revisions and Major or Minor Modifications to an Approved REMS

1. REMS Revisions:

a. Within ten days of receipt, ensure the incoming submission is correctly characterized based upon the proposed changes meeting the criteria for REMS revisions (as defined in FDA guidance) and closes submission out with a Product Correspondence final review memo. **[Product Office RPM]**

    i. Note: an applicant submitted change **only** to the REMS supporting document is neither a REMS revision nor a REMS modification and should be submitted as a product correspondence and reviewed by an assigned Pharmacovigilance Reviewer for close-out.

b. Submit **all** REMS materials and the REMS document (not the REMS Supporting Document) to OCOD for a disclosure review (use email: CBER-OCOD-Action Packages). OCOD will submit the material for posting on to FDA REMS Website. Note: REMS materials are to be posted within 14 days of receipt of the REMS revisions by applicant. **[Product Office RPM]**

2. Minor Modifications Submitted as CBE-30:

a. Ensure the incoming submission is correctly characterized as minor based upon the proposed changes meeting the criteria for minor REMS modifications (as defined in FDA guidance) and contact the OBPV RPM and OBPV Division Director to obtain OBPV reviewer (Pharmacovigilance Reviewer) assignment. The product office clinical reviewer should be notified of the submission receipt; however, a generated review is not generally necessary. The clinical reviewer may attend review team meeting(s) and provide clinical input if needed. Send the acknowledgement letter within 14 days of receipt. **[Product Office RPM]**

b. Determine whether CDER/OSE/DRM should be consulted and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

i. If CDER/OSE/DRM is to be consulted, send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

c. Perform initial review of the REMS modification. A request for information should only be made to the applicant through the Product Office RPM to provide any missing information essential to evaluate the REMS' effectiveness. **[Pharmacovigilance Reviewer]**

d. Complete the primary review no later than day 45. Send any comments to the Product Office RPM to communicate to applicant any needed changes to the REMS document and supporting document . Notify the Product Office Clinical Reviewer and the Product Office RPM at the time of final review upload. **[Pharmacovigilance Reviewer]**

e. Draft, circulate, and obtain final concurrence of the CR or approval letter no later than day 50 of the supplement receipt. **[Product Office RPM]**

f. Communicate the CR or approval letter to the applicant no later than day 60 of the supplement receipt. For an approval, submit <u>all</u> REMS materials and the REMS document (not the REMS Supporting Document) to OCOD for a disclosure review (use email: CBER-OCOD-Action Packages) and the coordination of posting of materials on the FDA REMS Website. Note: REMS materials are to be posted within three days of the approval date. **[Product Office RPM]**

3. Major Modifications Submitted (Not Due to Safety labeling Changes) as Prior Approval Supplement (PAS):

a. Ensure the incoming submission is correctly characterized as major based upon the proposed changes meeting the criteria for major REMS modifications (as defined in FDA guidance) and contact the OBPV RPM and OBPV Division Director to obtain OBPV reviewer (Pharmacovigilance Reviewer) assignment. A Product Office Clinical Reviewer should be

assigned. Send the supplement acknowledgement letter within 14 days of receipt. Schedule a planned REMS meeting with the review team around the 3 month mark of the supplement receipt. **[Product Office RPM]**

b. Consult CDER/OSE/DRM and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

i. Send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

c. Perform initial review of the REMS modification. A request for information should be made to the applicant through the Product Office RPM to provide any missing information essential to evaluate the REMS effectiveness. **[Pharmacovigilance Reviewer]**

d. Schedule the REMS meeting. Consult R 910.02: Attendee Table for BLA/NDA Meetings on who from the review team to invite. **[Product Office RPM]**

e. Facilitate the REMS meeting. The Product Office and OBPV should be prepared to discuss the major safety findings and the risk/benefit profile of the product in context of the proposed modification to the REMS. A goal should be to reach preliminary consensus **prior** to presenting at a CBER SWG meeting. **[Product Office RPM]**

f. Present changes to CBER SWG not later than month four of receipt:

i. Notify the Executive Secretary of the CBER SWG for scheduling. **[Office SWG Representative]**

ii. One week prior to the scheduled meeting, send the REMS background materials which will provide an overview of the product, safety risk that the REMS will mitigate, and proposed REMS changes to the CBER SWG Executive Secretary. **[Clinical and/or Pharmacovigilance Reviewers]**

The CBER SWG meeting provides decisional concurrence on the proposed modifications.

g. Complete the primary review by one month prior to the target action date. Send any comments to the Product Office RPM to communicate to applicant any needed changes to the REMS document and supporting document. Notify the Product Office Clinical Reviewer and the Product Office RPM at the time of final review upload. **[Pharmacovigilance Reviewer]**

h. Draft the REMS Modification Review Memorandum only if the modifications include: Modifying the Goal, adding one or more elements to

the REMS (i.e., MG, CP, ETASU), removing one, or more, or ALL elements of the REMS (this includes eliminating all REMS requirements). **[Clinical Reviewer]**

i. Send the draft REMS document and any attestations, if applicable to CDER/OSE/DRM for review at least five weeks prior target action date. **[Product Office RPM]**

i. If the modifications are to an ETASU REMS, after notification from the Product Office RPM of CDER/OSE/DRM review and acceptance, send the above materials and the draft REMS Modification Review Memo (if applicable to changes to ETASUs) to OCC for clearance only if needed (see Section V. Policy, D.) and allow at least four weeks prior to target action date. **[SWG Executive Secretary]**

j. Provide the REMS document to the applicant for review at least one week prior to the PDUFA or target action date. **[Product Office RPM]**

k. Finalize the REMS Modification Review Memorandum if applicable and obtain final concurrence. **[Clinical Reviewer]**

l. Draft, circulate, and obtain final concurrence of the CR or approval letter as appropriate no later than one week prior to the action target date. Note: Confirm any need for a CBER Safety Communication with OBPV and Product Office leadership. **[Product Office RPM]**

m. Communicate the CR or approval letter to the applicant by day 180 of supplement receipt. For an approval, submit **all** REMS materials and the REMS document (not the REMS Supporting Document) to OCOD for a disclosure review (use email: CBER-OCOD-Action Packages). OCOD will submit the material for posting of approved materials to the FDA REMS Website. Note: REMS materials are to be posted within three days of the approval date **[Product Office RPM]**.

4. Major Modifications Submitted as Part of an Efficacy Supplement:

a. Discuss the need for REMS modifications as a condition for approval at the filing meeting. If the application is to be filed, request that the Product Office RPM schedule an internal REMS meeting with OBPV no later than two weeks prior to the mid-cycle meeting. **[Pharmacovigilance Reviewer]**

b. Determine whether CDER/OSE/DRM should be consulted and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

i. Send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

c. Schedule the REMS meeting. Consult R 910.02: Attendee Table for BLA/NDA Meetings on who from the review team to invite. **[Product Office RPM]**

d. Facilitate the REMS meeting. The Product Office and OBPV should be prepared to discuss the major safety findings and the risk/benefit profile of the product in context of the proposed indication and needed REMS modifications. **[Product Office RPM]**

e. Present changes to CBER SWG no later than one month prior to the PDUFA or target action date:

i. Notify the Executive Secretary of the CBER SWG for scheduling. **[Office SWG Representative]**

ii. One week prior to the scheduled meeting, send the REMS background materials which will provide an overview of the product, safety risk that the REMS will mitigate, and proposed REMS changes to the CBER SWG Executive Secretary. **[Clinical and/or Pharmacovigilance Reviewers]**

The CBER SWG meeting provides decisional concurrence on the proposed modifications.

f. Complete the reviews no later than one month prior to the PDUFA or target action date. Send any comments to the Product Office RPM to communicate to applicant any needed changes to the REMS document and supporting document. **[Clinical Reviewer and Pharmacovigilance Reviewer]**

g. Complete the REMS Modification Review Memorandum only if the modifications include: modifying the goal, adding, one or more elements to the REMS (i.e., MG, CP, ETASU), removing one, or more, or all elements (i.e., MG, CP, ETASU) of the REMS (this includes releasing all REMS requirements). **[Clinical Reviewer]**

h. Send the draft REMS document and any attestations, if applicable to CDER/OSE/DRM for review at least five weeks prior to the target action date. **[Product Office RPM]**

i. If the modifications are to an ETASU REMS, after notification from the Product Office RPM of CDER/OSE/DRM review and acceptance, send the above materials and the draft REMS Modification Review Memo (if applicable to changes to ETASUs) to OCC for clearance only if needed (see Section V. Policy, D.) and allow at least four weeks prior to target action date. **[SWG Executive Secretary]**

i. Provide the REMS document to the applicant for review at least one week prior to the PDUFA or target action date **[Product Office RPM]**

j. Finalize the REMS Modification Review Memorandum if applicable and obtain final concurrence. **[Clinical Reviewer]**

k. No later than one week prior to the supplement PDUFA or action date, draft, circulate, and obtain final concurrence of the CR or approval letter containing REMS template language as appropriate. **[Product Office RPM]**

l. Communicate the CR or approval letter to the applicant by the supplement PDUFA or target action date. For an approval, submit **all** REMS materials and the REMS document (not the REMS Supporting Document) along with the Transmittal memo, approval letter and Package Insert to OCOD for a disclosure review (use email: CBER-OCOD-Action Packages) and the coordination of posting of approved REMS materials on the FDA REMS Website. Note: REMS materials are to be posted within three days of the approval date. **[Product Office RPM]**

5. Major Modifications Submitted Due to Safety labeling Changes) as Prior Approval Supplement (PAS):

a. Ensure the incoming submission is correctly characterized as either a conforming (60-day review clock) or non-conforming REMS modification (180-day review clock) based upon the proposed changes meeting the criteria defined in the FDA guidance and contact the OBPV RPM and OBPV Division Director to obtain OBPV reviewer (Pharmacovigilance Reviewer) assignment. A Product Office Clinical Reviewer should be assigned. A REMS meeting is not necessary for a conforming REMS modification; however, a REMS meeting with the review team should be scheduled for a non-conforming REMS modification around the 3 month mark of the supplement receipt. Note: Acknowledgment letters are not sent for these types of supplements **[Product Office RPM]**

b. Consult CDER/OSE/DRM and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

i. Send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

c. Perform initial review of the REMS modification. A request for information should be made to the applicant through the Product Office RPM to provide any missing information essential to evaluate the REMS effectiveness. **[Pharmacovigilance Reviewer]**

d. Schedule the REMS meeting ***if a non-confirming REMS modification***. Consult R 910.02: Attendee Table for BLA/NDA Meetings on who from the review team to invite. **[Product Office RPM]**

e. Facilitate the REMS meeting. The Product Office and OBPV should be prepared to discuss the major safety findings and the risk/benefit profile of the product in context of the proposed modification to the REMS. A goal should be to reach preliminary consensus prior to presenting at a CBER SWG meeting. **[Product Office RPM]**

f. Present non-conforming REMS changes to CBER SWG not later than month four of receipt:

i. Notify the Executive Secretary of the CBER SWG for scheduling. **[Office SWG Representative]**

ii. One week prior to the scheduled meeting, send the REMS background materials which will provide an overview of the product, safety risk that the REMS will mitigate, and proposed REMS changes to the CBER SWG Executive Secretary. **[Clinical and/or Pharmacovigilance Reviewers]**

The CBER SWG meeting provides decisional concurrence on the proposed non-conforming modifications.

g. Complete the primary review by two weeks prior to the target action date for a conforming REMS modification or one month prior to the target action date for a non-conforming modification. Send any comments to the Product Office RPM to communicate to applicant any needed changes to the REMS document and supporting document. Notify the Product Office Clinical Reviewer and the Product Office RPM at the time of final review upload. **[Pharmacovigilance Reviewer]**

h. Draft the REMS Modification Review Memorandum only if the modifications include: Modifying the Goal, adding one or more elements to the REMS (i.e., MG, CP, ETASU), removing one, or more, or ALL elements (i.e., MG, CP, ETASU) of the REMS (this includes releasing all REMS requirements). **[Clinical Reviewer]**

i. Send the draft REMS document and any attestations, if applicable to CDER/OSE/DRM for review at least two weeks prior to the action date for a conforming REMS modification or 5 weeks prior to the action date for a non-conforming REMS modification. **[Product Office RPM]**

i. If the modifications are to an ETASU REMS, after notification from the Product Office RPM of CDER/OSE/DRM review and acceptance, send the above materials and draft REMS Modification Review Memo (if

applicable to changes to ETASUs), to OCC for clearance only if needed (see Section V. Policy, D.) and allow at least two weeks prior to target action date. **[SWG Executive Secretary]**

j. Provide the REMS document to the applicant for review at least one week prior to the PDUFA or target action date. **[Product Office RPM]**

k. Finalize the REMS Modification Review Memorandum if applicable and obtain final concurrence. **[Clinical Reviewer]**

l. Draft, circulate, and obtain final concurrence of the CR or approval letter as appropriate no later than one week prior to the action target date. **[Product Office RPM]**

m. Communicate the CR or approval letter to the applicant by the action target date. For an approval, submit **all** REMS materials and the REMS document (not the REMS Supporting Document) to OCOD for a disclosure review (use email: CBER-OCOD-Action Packages) and the coordination of posting of approved materials on the FDA REMS Website . Note: REMS materials are to be posted within three days of the approval date **[Product Office RPM]**.

6. Modifications Requested by CBER:

a. If a REMS modification is believed to be necessary to 1) ensure the benefits continue to outweigh the risks or 2) to minimize burden on the healthcare system complying with the REMS, the Product Office RPM should schedule a REMS meeting as soon as possible between the Product Office and OBPV to reach consensus.

b. Consult CDER/OSE/DRM and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

i. Send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

c. Schedule the REMS meeting. Consult R 910.02: Attendee Table for BLA/NDA Meetings on who from the review team to invite. **[Product Office RPM]**

d. Facilitate the REMS meeting. The Product Office and OBPV should be prepared to discuss the major safety findings and the risk/benefit profile of the product in context of the proposed modification to the REMS. A goal should be to reach preliminary consensus prior to presenting at a CBER SWG meeting. **[Product Office RPM]**

e. Notify the Executive Secretary of the CBER SWG so that discussion can occur at the earliest possible SWG.

i. One week prior to the scheduled CBER SWG meeting, send the related background materials which can include providing an overview of product, the safety risks, and justification for a REMS modification to the SWG Executive Secretary. **[Pharmacovigilance Reviewer, or designees]**

The CBER SWG meeting provides decisional concurrence on the need for the proposed REMS modification.

f. Complete the REMS Modification Review Memo if the needed modifications include: modifying the goal, adding, one or more elements to the REMS (i.e., MG, CP, ETASU), removing one, or more, or all elements (i.e., MG, CP, ETASU) of the REMS (this includes releasing all REMS requirements). **[Clinical Reviewer]**

g. Draft, circulate, and obtain concurrence of the REMS Modification Notification Letter (which will communicate the rationale for the needed changes and the type of modification needed, i.e., CBE-30 or PAS). **[Product Office RPM]**

i. If modifications are to an ETASU REMS, see Section V. Policy, D. on whether to perform OCC clearance.

h. Communicate the letter to the applicant. **[Product Office RPM]**

i. Ensure the incoming REMS submission is properly characterized and follow processes above depending on type of modification. **[Product Office RPM]**

C. REMS Assessments

1. Ensure the incoming submission is correctly characterized as a product correspondence and contact the OBPV RPM and OBPV Division Director to obtain OBPV reviewer (Pharmacovigilance Reviewer) assignment. **[Product Office RPM]**

Note: If the applicant submitted a proposed minor modification (CBE-30) in the same submission as the assessment, request that the applicant unbundle and submit the modification separately. A major modification (PAS), with the exception of a conforming REMS modification, can be submitted with the assessment as the review clocks are similar. The product office clinical reviewer should be notified of the submission receipt; however, a generated review is not generally necessary. The clinical reviewer may attend review team meeting(s) and provide clinical input if needed. Refer to major modification process above.

2. Schedule a planned initial REMS meeting with the review team around 90 days after assessment receipt. Consult R 910.02: Attendee Table for

BLA/NDA Meetings on who from the review team to invite. **[Product Office RPM]**

3. Perform initial review of the REMS assessment. A request for any needed information should be made to the applicant through the Product Office RPM to provide any missing information essential to evaluate the REMS effectiveness. **[Pharmacovigilance Reviewer]**

    a. If the REMS assessment is determined to be incomplete, notify the RPM to send a letter to the applicant to submit the missing information. **[Pharmacovigilance Reviewer]**

4. Determine whether CDER/OSE/DRM should be consulted and notify the Product Office RPM. **[Pharmacovigilance Reviewer]**

    a. Send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

5. Conduct the REMS meeting to discuss the preliminary internal review of the assessment. OBPV should be prepared to discuss the major findings of the assessment. **[Product Office RPM]**

6. Complete the draft review no later than month four of the assessment receipt and circulate to attendees of the internal REMS meeting for comments prior to the CBER SWG meeting. **[Pharmacovigilance Reviewer]**

7. Present the assessment findings at a CBER SWG Meeting, as needed, by month 4 of assessment receipt:

    Note: For REMS assessments for which OBPV has identified no major noncompliance issues (or if this is a the applicant's first REMS assessment and not enough information is available to determine whether the REMS is meeting its goals), OBPV should first provide their review memo to the SWG Executive Secretary to assess with the SWG co-chairs whether a presentation is beneficial or should be deferred to review of future assessments. If a presentation is determined not to be needed, the OBPV review memo will be shared with the SWG members.

    a. Notify the Executive Secretary of the CBER SWG for scheduling. **[Office SWG Representative]**

    b. One week prior to the scheduled meeting, send the REMS background materials which can include providing an overview of product, the safety risks that the REMS mitigates, the REMS elements, and review of the submitted REMS assessment on whether the REMS is meeting its goals. **[Pharmacovigilance Reviewer, or designees]**

8. Begin to finalize and obtain concurrence on the REMS assessment review memo no later than month five. **[Pharmacovigilance Reviewer]**

9. If the REMS assessment determined that the REMS is not meeting its goals and a REMS modification is necessary, the Pharmacovigilance Reviewer may need to reach out to the Clinical Reviewer as a REMS modification memo may be needed (with OCC clearance depending if an ETASU REMS). Refer to "Revisions and Major or Minor Modifications to an Approved REMS/Modifications Requested by CBER" section of this SOPP. **[Pharmacovigilance Reviewer]**

10. One week prior to the target action date, draft, circulate, and obtain final concurrence of the appropriate REMS Assessment Acknowledgement Letter. **[Product Office RPM]**

11. Draft, circulate, finalize, and communicate the letter to the applicant by the target action date. **[Product Office RPM]**

D. Review of Received REMS Assessment Instruments and Methodology

1. Ensure the incoming submission is correctly characterized as a "Product Correspondence-REMS Assessment Instruments and Methodology" and contact the OBPV RPM and OBPV Division Director to obtain Pharmacovigilance Reviewer assignment. The product office clinical reviewer should be notified of the submission receipt; however, a generated review is not generally necessary. The clinical reviewer may attend review team meeting(s) and provide clinical input if needed. **[Product Office RPM]**

2. Perform initial review and a request for information should be made to the applicant through the Product Office RPM to provide any missing information essential to evaluate the submitted materials. **[Pharmacovigilance Reviewer]**

3. Determine whether CDER/OSE/DRM should be consulted and notify the Product Office RPM within 14 days of receipt. **[Pharmacovigilance Reviewer]**

    a. Send the request for consult via the ICCR process (see SOPP 8001.5). **[Product Office RPM]**

4. Finalize and obtain concurrence on the primary review no later than day 85. **[Pharmacovigilance Reviewer]**

5. Communicate via electronic correspondence any reviewer comments/recommendations to the applicant by day 90. Ensure it is entered into the appropriate regulatory system and uploaded into the correct

addmininstrative file. **Note:** A communication to at least confirm the review is complete is needed. **[Product Office RPM]**

E. Requiring a New REMS Based upon NSI

1. If a NSI issue has been identified post-approval, which in addition to a Safety Labeling Change (SLC) may require a new REMS to be instituted, schedule a REMS meeting as soon as possible with the Product Office and OBPV, and other appropriate regulatory staff, including CDER/OSE/DRM, to reach consensus. In addition, notify the Executive Secretary of the CBER SWG so that discussion can occur at the earliest possible SWG meeting. **[Product Office RPM]**

    a. One week prior to the scheduled CBER SWG meeting, send the related background materials, which can include an overview of product, the safety risks, and REMS justification. **[Pharmacovigilance Reviewer, or designees]**

    The CBER SWG meeting provides decisional concurrence on the need for a REMS.

2. If a REMS is needed, draft the REMS Review Memorandum. **[Clinical Reviewer]**

    a. If there is a need for an ETASU REMS send the draft REMS Review Memorandum to OCC for clearance at least four weeks prior to the target communication date to the applicant. **[SWG Executive Secretary]**

3. Draft, circulate, and finalize the REMS Notification Letter as soon as possible. Ensure the applicant has been informed of the FDA weblink to the REMS guidance materials and the REMS template to the applicant. **[Product Office RPM]**

    a. If this will be an ETASU REMS, the SWG Executive Secretary will clear the REMS Notification Letter with OCC before being sent to the applicant.

VIII. Appendix

A. Appendix A: REMS Review Timelines

IX. References

A. References below are CBER internal:

1. Regulatory Template T 910.05: Risk Evaluation and Mitigation Strategy (REMS) Review Memorandum

2. Regulatory Template T 910.17: Risk Evaluation and Mitigation Strategy (REMS) Modification Review Memorandum

3. R 910.02: Attendee Table for BLA/NDA Meetings

4. SOPP 8001.5: Inter-Center Consultative Review Process

B. References below are found on the Internet:

1. Food and Drug Administration Amendments Act of 2007 (FDAAA)

2. FDA Web Page: Approved Risk Evaluation and Mitigation Strategies (REMS)

3. Food and Drug Administration Safety and Innovation Act (FDASIA)

4. Draft Guidance for Industry: Format and Content of a REMS Document

5. REMS Document Template

6. Guidance for Industry: Risk Evaluation and Mitigation Strategies: Modifications and Revisions

7. Draft Guidance for Industry: REMS Assessment: Planning and Reporting

8. Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge

9. Guidance for Industry: REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

10. SOPP 8401.7: Action Package for Posting

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
E Laughner & M. Alimchandani	Katie Rivers, MS Chief, RABOB/DROP/ORO	October 27, 2025	6	Updated to clarify process for REMS eliminations.
E Laughner	Darlene Martin, MS, PMP ORO/DROP Director (acting)	September 28, 2022	5	Minor clarifications and update on REMS methodologies review clock for PDUFA VII.

Written/ Revised	Approved By	Approval Date	Version Number	Comment
E Laughner & M. Alimchandani	Christopher Joneckis, PhD	May 9, 2022	4	Clarifications on when OCC clearance is needed, when CDER DRM consultation is needed and when SWG presentations are needed. Incorporated organizational changes due to 2022 CBER reorganization.
M.Monser	N/A	December 11, 2020	3	Technical Update for retirement of the EDR.
E.Laughner	Christopher Joneckis, Ph.D.	February 17, 2020	2	Editorial change of CDER DRISK to DRM. Revision to reflect November 2019 policy change per FDAAA policy group regarding REMS Notification
E. Laughner	Christopher Joneckis, Ph.D.	November 21, 2019	1	First Issuance

SOPP 8417: Appendix A: REMS Review Timelines

Type of Incoming REMS Submission	FDA review clock	Hold REMS Meeting between OBPV and Product Office?	Product Office/OBPV Present at SWG Meeting?	Consult CDER DRM?
New REMS in Original Application	As per PDUFA goal	Yes	Yes	Yes
REMS Assessment	6 months	Yes	As needed*	As needed#
REMS Assessment Instruments or Methodology	90 days	No	No	As needed
REMS Revisions	5-days	No	No	As needed
Minor REMS Modification (CBE-30)	60-days	No	No	As needed
Major REMS Modification (PAS)- as part of efficacy supplement	As per PDUFA goal	Yes	Yes	As needed
Major REMS Modification (PAS) -not due to Safety labeling changes	180-days (not a PDUFA goal supplement)	Yes	Yes	As needed
Major REMS Modification (PAS)- due to Safety labeling changes- conforming	60-days (not a PDUFA goal supplement)	No	No	As needed
Major REMS Modification (PAS)- due to Safety labeling changes)- non-conforming	180-days (not a PDUFA goal supplement)	Yes	Yes	As needed

* For REMS assessments for which OBPV has identified no major noncompliance issues, OBPV should first provide their review memo to the SWG Executive Secretary to assess with the SWG co-chairs whether a SWG presentation is beneficial or should be deferred to review of future assessments.

#OBPV will determine whether CDER DRM should be consulted on REMS submissions