
POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

Determination of the Need for and Review of a New REMS

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PURPOSE

This MAPP describes the policy, responsibilities, and procedures to be used in the Center for Drug Evaluation and Research (CDER) to:

- determine whether a risk evaluation and mitigation strategy (REMS) for a prescription drug product¹ marketed under a new drug application (NDA) or biologics license application (BLA) is necessary to ensure that the benefits of the drug product outweigh its risks
- review a ***proposed-REMS submission***² developed by an applicant³ for an NDA or BLA to determine if it is acceptable⁴

¹ For the purposes of this MAPP, *drug product* means human drug and biological products regulated by CDER, unless otherwise specified.

² Terms that appear in ***bold italic*** type upon first use are defined in the Definitions section.

³ For the purpose of this MAPP, *applicant* means any person that holds an application approved under section 505 of the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) or a license issued under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) for a drug product, or that submits a new drug application (NDA), a biologics license application (BLA), or an amendment or supplement to an NDA or BLA to obtain FDA approval.

⁴ Applies to proposed REMS voluntarily submitted by the applicant and those submitted in response to the Agency's communication to the applicant of the REMS requirements.

This MAPP applies to a new REMS being developed at either the preapproval or postapproval stage. This MAPP does not pertain to a shared system REMS⁵ developed by multiple applicants for NDAs, ANDAs, and BLAs, nor does it apply to modifications to an approved REMS.⁶

BACKGROUND

The Food and Drug Administration Amendments Act of 2007 (FDAAA)⁷ created section 505-1 of the Food, Drug, and Cosmetic Act (FD&C Act), which authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug product outweigh its risks.⁸ A REMS is a required risk management strategy that employs tools beyond the prescribing information.

FDA can require a REMS either at the time of approval of a prescription NDA or BLA or after approval, if FDA becomes aware of new safety information.⁹ A REMS may include one or more of the following components:

- A Medication Guide or patient package insert to provide risk information to patients.^{10, 11}
- A communication plan to disseminate risk information to health care providers.¹²
- Certain packaging and safe disposal technologies for drug products that pose a serious risk of abuse or overdose.¹³
- Elements to Assure Safe Use (ETASU) to mitigate specific serious risks associated with a drug product.¹⁴ Examples of ETASU include a requirement that health care providers who prescribe the drug product have specialized training, that patients using the drug product be monitored, and that the drug product be dispensed only with evidence of safe-use conditions.
- An implementation system through which an applicant can monitor and evaluate implementation of certain ETASU by healthcare providers, pharmacists, and other responsible parties.¹⁵

⁵ MAPP 6701.3 *Development of a Single, Shared System (SSS) Risk Evaluation and Mitigation Strategy (REMS) or a Separate REMS with Elements to Assure Safe Use (ETASU): Responsibilities and Procedures*

⁶ MAPP 4191.1 *Risk Evaluation and Mitigation Strategies Modifications and Revisions.*

⁷ Public Law 110-85.

⁸ Section 505-1(a) of the FD&C Act.

⁹ Section 505-1(b)(3) of the FD&C Act.

¹⁰ Section 505-1(e)(2) of the FD&C Act.

¹¹ Guidance for Industry: *Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*. We update guidances periodically. For the most recent version of a guidance, see

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹² Section 505-1(e)(3) of the FD&C Act.

¹³ Section 505-1(e)(4) of the FD&C Act.

¹⁴ Section 505-1(f)(3) of the FD&C Act.

¹⁵ Section 505-1(f)(4) of the FD&C Act.

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- For REMS for NDAs and BLAs, a timetable for the submission of assessments by the applicant that describes the extent to which the REMS is meeting its goals.¹⁶

FDAAA requires FDA to consider the following 6 factors¹⁷ in deciding whether to require a REMS for a drug product at approval:

- The estimated size of the population likely to use the drug product involved.
- The seriousness of the disease or condition that is to be treated with the drug.
- The expected benefit of the drug product with respect to the disease or condition.
- The expected or actual duration of treatment with the drug product.
- The seriousness of any known or potential adverse events that may be related to the drug product and the background incidence of such events in the population likely to use the drug product.
- Whether the drug product is a new molecular entity.

These 6 factors influence FDA's decisions with respect to whether a REMS is required for a drug product and the components of the REMS.¹⁸

POLICY

- CDER's Office of Surveillance and Epidemiology (OSE) and Office of New Drugs (OND) will jointly determine the need for and the components of the REMS for a prescription drug product approved under an NDA or BLA.¹⁹
- CDER will consider the statutory factors in determining if a REMS is necessary.
- A proposal for a REMS with ETASU will be discussed with the REMS Oversight Committee (ROC).

¹⁶ Section 505-1(d) of the FD&C Act.

¹⁷ Section 505-1(a)(1) of the FD&C Act requires that FDA consider these factors in determining whether a REMS is necessary for a drug at initial approval. FDA also generally considers these factors in determining whether, based on new safety information, a REMS is necessary for a drug that is the subject of an approved application.

¹⁸ Guidance for Industry: *Application of Statutory Factors in Determining When a REMS Is Necessary*

¹⁹ Sections 505-1(a)(1) and 505-1(c)(2) of the FD&C Act requires "consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety with respect to the drug" to determine that a REMS is necessary to ensure that the benefits of the drug outweigh the risks of the drug product, and to determine what elements should be included in the REMS. CDER interprets the FDAAA language to mean that OSE and OND will jointly decide on a REMS, including other FDA groups as needed. Staff from OSE's Division of Risk Management must be included on the team making the decision about the need for a REMS and its elements.

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- Decisions regarding the need for a REMS, the components of the REMS, and the review of the proposed REMS submission will be made in accordance with CDER's policy on equal voice and dispute resolution.^{20,21}
 - Once CDER determines that a REMS is necessary, CDER will not approve an application or an efficacy supplement without an acceptable REMS.
 - If CDER determines in the pre-approval stage that a REMS is necessary for approval, a **REMS Memorandum (Memo)** will be written and signed by the OND Deputy Director for Safety (DDS) or the Associate Director for Safety (ADS) prior to the time the **action letter** is issued.
 - If, after a drug product is approved, CDER determines that a REMS is necessary:
 - CDER will issue a **REMS Notification Letter** to the applicant informing them of the requirement to submit a proposed-REMS submission.
 - A REMS Memo will be written and signed by the OND DDS or ADS prior to the time that the REMS Notification letter is issued.
 - If CDER determines that changes must be made to a proposed REMS or REMS requirements have changed from what was specified in the REMS Notification Letter, a **REMS Element Retraction-Addition Letter** will be issued to the applicant.
 - CDER will review and act on the proposed-REMS submission according to application goal dates.²²
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RESPONSIBILITIES

Typically, the following CDER offices contribute to the REMS activities described in this MAPP: OSE, OND, Office of Compliance (OC), Office of Communications (OCOMM), Office of Medical Policy (OMP), and Office of Regulatory Policy (ORP). This section describes the responsibilities of staff with key roles in the process.

OSE Division of Risk Management (DRM) Risk Management Analyst (RMA)

- Serves as the REMS subject matter expert on the **Pre- and Postapproval REMS Review Team** (referred throughout as **REMS Review Team**).

²⁰ MAPP 4151.8 *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*.

²¹ MAPP 4151.1 Rev 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*.

²² Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures Fiscal Years 2018-2022, available at <https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf>

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- Reviews proposed-REMS submissions from the applicant, including the **REMS Document**, **REMS Materials**, and **REMS Supporting Document**.
 - Prepares the background document and presentation, with input from the REMS Review Team, for all ROC meetings that discuss a proposed REMS.
 - Prepares the background document and presentation for advisory committee in consultation with the OND review division.
 - Prepares **letter-ready comments** on the proposed REMS based on the REMS Review Team recommendations.
 - Writes and archives the DRM REMS review that describes the acceptability of the proposed REMS submission, incorporating the recommendations of the REMS Review Team.

OSE DRM RMA Team Leader (TL)

- Ensures timely review of the proposed REMS submissions.
- Identifies, with input from DRM Management and other CDER offices, whether the ROC and/or an advisory committee will need to provide advice on a proposed REMS.
- Identifies, with input from DRM Management, the need to consult with other OSE Divisions and CDER offices.

OSE DRM Health Communications Analyst (HCA)

- Identifies and recommends health education and communication options to include in a REMS.
- Reviews proposed REMS Materials submitted as part of a proposed REMS submission.

OSE DRM REMS Assessment Analyst (RAA) and RAA TL

- Provides expertise on the metrics and other aspects of the **REMS Assessment Plan**.
- Identifies, with input from DRM management, the need to consult with other OSE Divisions and CDER offices on the REMS Assessment Plan.
- Reviews the proposed REMS Assessment Plan submitted as part of a proposed REMS submission.

OSE DRM Quality Assurance (QA) Analyst

- Reviews the REMS Document for consistency with other REMS and REMS Document template.
- Reviews the REMS Document to identify potential policy and legal issues for input from the Office of Regulatory Policy.

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- Provides the REMS Document for REMS with ETASU and REMS Attestations to the Office of Regulatory Policy and Office of Chief Counsel for their review.

OSE DRM Division Director (DD) or designee

- Ensures acceptability of the final REMS Document, REMS Materials, and REMS Supporting Document.
- Concurs and finalizes the DRM REMS review.

OSE Safety Regulatory Project Manager (SRPM)

- Schedules REMS Review Team meetings.
- Works with DRM staff and the REMS Review Team to ensure REMS review deadlines align with application goal dates.
- Works with the DRM RMA and RMA TL to request ROC meetings, as needed.

OND Clinical Review Team

- Reviews and provides input on the clinical aspects of the proposed REMS program.

OND Deputy Director for Safety (DDS)/Associate Director for Safety (ADS)

- Oversees the OND review division activities regarding the REMS proposal.
- Reviews the clinical aspects of the proposed REMS and provides input on clinical requirements.
- Completes a REMS Memo documenting CDER's evaluation of the 6 factors that FDA must consider when deciding whether to require a REMS.
- Serves as the signatory authority for action letters and other REMS-related letters, including the REMS Notification Letter and the REMS Element Retraction-Addition Letter, for NDA/BLA products.

OND Safety Regulatory Project Manager (SRPM)

- Reviews REMS section of action letters for REMS established in the preapproval setting.
- Attends milestone meetings for original applications and efficacy supplements.
- Schedules post-approval application review meetings where the REMS will be discussed.
- Serves as the point of contact regarding the proposed REMS in the post-approval setting.
- During post-approval REMS determination and review, drafts REMS-related correspondence (e.g., information requests, REMS Notification letter, and action letter).

- Facilitates clearance of all REMS-related correspondences.

OND Regulatory Project Manager (RPM)

- Schedules preapproval application review meetings (e.g., milestone meetings, JAM meetings), including meetings where the REMS may be discussed.
- Serves as the point of contact for the NDA/BLA applicant regarding the proposed REMS in the preapproval setting.
- During preapproval application review, drafts REMS-related correspondence (e.g., information requests, discipline review letters).
- Drafts action letters for original NDA/BLA and efficacy supplements that include a REMS.

OMP Office of Prescription Drug Promotion (OPDP) Regulatory Review Officer

- Reviews proposed REMS Materials submitted as part of a proposed REMS to ensure that it is not promotional.

OC Consumer Safety Officer

- Provides compliance advice on the proposed REMS.
- Evaluates the proposed REMS document to assess whether it is written in a manner that is enforceable.
- Determines if the proposed REMS is submitted within established timelines.

ORP Regulatory Counsel

- Provides policy advice on proposed REMS.
- Identifies policy issues that arise during the review of a proposed REMS and prepares policy issue papers for discussion at a ROC meeting or a FDAAA Policy Group meeting.²³
- Leads policy discussions that arise during the review of the proposed REMS.
- Identifies issues that arise during the development of a proposed REMS that require legal input.

REMS Oversight Committee (ROC)

- Provides CDER senior leadership advice on the recommendations made by the REMS Review Team to address application-specific REMS issues.

²³ FDAAA Policy Group is a CDER workgroup that ensures consistent and appropriate implementation of the postmarketing safety authorities and requirements in the FD&C Act, as amended by the Food and Drug Administration Amendments Act of 2007 and the 2012 Food and Drug Safety and Innovation Act. It provides input on novel, unresolved, and/or complex REMS, safety labeling changes, and postmarketing requirements issues that require legal input and/or have CDER-wide policy implications.

Safety Requirements Team (SRT)

- Clears REMS action letters, other REMS-related letters, and REMS Memo, if applicable.

ORP Division of Information Disclosure Policy (DIDP)

- Reviews and redacts the REMS Document and REMS Materials.
- Provides redacted documents to the Division of Online Communications in the Office of Communications (OCOMM) for posting on the FDA's REMS@FDA website.

OCOMM Division of Drug Information (DDI)

- Ensures that the approved REMS is posted on FDA's REMS@FDA website.

PROCEDURES**A. Pre-Approval REMS Determination and Review²⁴****1. Pre-Submission Activities (e.g., pre-NDA/BLA Meetings)**

- 1.1. The OND RPM notifies the OSE SRPM²⁵ that a meeting request with the applicant has been granted.
- 1.2. The OSE SRPM and the DRM TL determine DRM's involvement, and if it is determined that DRM should attend the meeting, the OSE SRPM provides the OND RPM the list of meeting attendees from OSE.
- 1.3. The OND RPM provides the meeting background package and other pre-submission documents to the OSE SRPM for distribution.²⁶
- 1.4. The DRM RMA reviews the background package, drafts preliminary responses to any REMS-related questions, and clears these responses through the DRM TL and DRM Director or designee.
- 1.5. The DRM RMA provides the cleared preliminary responses to the OND RPM on a shared site or by email, with a copy to the OSE SRPM.
- 1.6. The DRM RMA and DRM TL attend the pre-meeting for the pre-NDA/BLA meeting to discuss the preliminary response with OND.
- 1.7. The DRM RMA and DRM TL attend the pre-NDA/BLA meeting with the sponsor to address any questions related to the need for a REMS.

²⁴ See footnote 4.

²⁵ The OND RPM notifies the OSE SRPM via one of a variety of ways, including, but not limited to: email, electronic meeting invitation, phone, etc.

²⁶ The OND RPM provides the meeting background package to the OSE SRPM via one of a variety of ways, including, but not limited to: a hyperlink to the location (i.e., server path), a hard copy, an attachment to the meeting invitation.

2. Application Submission

- 2.1. The OND RPM notifies the OSE SRPM²⁷ of the submission of an NDA or BLA.
- 2.2. The OSE SRPM ensures that the appropriate DRM staff are added to the *Marketing Application Review Team* and are included in all Marketing Application Review Team meetings, as appropriate (see Attachment 1).
- 2.3. If the applicant submitted a proposed REMS, voluntary risk mitigation strategy, risk management plan, or Risk Minimization Action Plan²⁸:
 - 2.3.1. The DRM RMA will conduct a high-level review.
 - 2.3.2. The DRM RMA drafts letter-ready comments to include in the *Filing Review Issues Identified letter*, if needed (e.g., CDER determines that a REMS is required, or the applicant's proposed REMS has deficiencies) and clears the comments through the DRM TL and DRM Director or designee.
 - 2.3.3. The DRM RMA provides the DRM comments for the Filing Review Issues Identified letter to the OND RPM on a shared site or by email with a copy to the OSE SRPM.
- 2.4. The OND RPM includes the DRM comments, as well as comments from other CDER Offices that have been cleared with the OND review division, in the Filing Review Issues Identified letter and sends that letter to the applicant.

3. Determining the Need for a REMS²⁹

- 3.1. The Marketing Application Review Team will meet to discuss the application as described in the Integrated Review of Marketing Applications Process How-to-Guide.³⁰
- 3.2. The Marketing Application Review Team will begin discussing any safety findings related to the drug product at the Benefit-Risk Scoping Meeting.³¹ Further discussion of safety-related review issues will continue at Joint

²⁷ See footnote 25.

²⁸ Applicants may voluntarily submit a proposed REMS without having been required to do so by FDA. If an applicant voluntarily submits a proposed REMS, it is not a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks. Additionally, some applicants may submit a voluntary risk mitigation proposal, risk management plan, or Risk Minimization Action Plan these measures can be performed outside of a REMS. If FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks, FDA will inform the applicants that submitted a voluntary risk mitigation strategy, risk management plan, or Risk Minimization Action Plan, to submit a proposed REMS.

²⁹ Not all tasks occur sequentially; some tasks may occur simultaneously.

³⁰ The Integrated Review of Marketing Applications: How-to-Guide supports Marketing Application Review Teams throughout the NDA/BLA review process (from pre-NDA/BLA phase through regulatory action).

³¹ The Benefit-Risk Scoping Meeting is an internal CDER meeting that has been implemented as part of the Marketing Application Review process.

- Assessment Meetings³² and/or other milestone meetings. If a serious safety issue is identified at any point during the application review, a REMS Review Team will be established by OSE.
- 3.3. The DRM RMA will present the applicant's proposed REMS or risk management plan and/or the REMS Review Team's current thinking of the risk management strategy at the Midcycle Meeting.
 - 3.4. If the Marketing Application Review Team and REMS Review Team determine that a REMS:
 - 3.4.1. Is not necessary, the DRM RMA will draft a primary review³³ that documents the rationale for not requiring a REMS, upload the review in the CDER electronic document archiving system, and provide recommendations to the Marketing Application Review Team to incorporate into the interdisciplinary review for the NDA or BLA.
 - 3.4.2. Is necessary, the DRM RMA will draft a primary review³⁴ that documents the rationale for the proposed REMS and upload the review in the CDER electronic document archiving system or include that rationale in the final DRM review (see section A. 5.1 below).
 - 3.5. The OSE SRPM will schedule team meetings for the REMS Review Team to discuss the necessary components of the REMS, as needed.
 - 3.6. The DRM RMA and TL will determine if any issues require input from the ROC.
 - 3.6.1. The OSE SRPM will work with the appropriate Office of the Center Director (OCD) staff to schedule the ROC meeting.
 - 3.6.2. To prepare for the ROC meeting, the OSE SRPM will schedule REMS Review Team meetings, if necessary.
 - 3.6.3. The REMS Review Team will attend the scheduled ROC meeting and present their proposal.
 - 3.6.4. The REMS Review Team will update the Marketing Application Review Team on the outcome of the ROC meeting and coordinate any REMS-related issues with the Marketing Application Review Team.

³² The Joint Assessment Meeting is an internal CDER meeting that has been implemented as part of the Integrated Review of Marketing Applications Review process.

³³ DRM writes a primary review in the following instances:

- The drug product is a new molecular entity, regardless of whether a proposed REMS is included in the application
- The applicant submits a proposed REMS with the application
- The drug product already has an approved REMS and the applicant is requesting approval of a new indication (i.e., the applicant has submitted an efficacy supplement)
- The drug product will be part of a class of drugs that already has a REMS
- Certain 505(b)(2) or biosimilar applications that have unique serious risks warranting consideration of a REMS.

³⁴ See footnote 33.

- 3.7. The OND RPM will communicate the REMS requirements to the applicant^{35, 36} as early as possible and document and upload this communication in CDER's electronic document archiving system in the following circumstances:
- The applicant voluntarily submitted a proposed REMS submission and CDER has determined that a proposed REMS is not necessary.
 - The applicant voluntarily submitted a proposed REMS submission but did not include all the necessary elements.
 - The applicant did not propose a REMS, but CDER has determined that a REMS is necessary.
 - CDER initially communicated to the applicant that a REMS is necessary but subsequently determined that it is no longer necessary, or the REMS requirements have changed.
 - CDER determines that a REMS is required for a drug product seeking a new indication as part of an efficacy supplement based on new safety information.

4. Review of Proposed REMS

- 4.1. DRM RMA, HCA, and RAA will initiate review of the proposed REMS submission, which includes one or more of the following activities in accordance with application goal dates:
- 4.1.1. Ensure that the proposed REMS submission is complete (i.e., includes the REMS document, REMS materials, and REMS supporting document).
 - 4.1.2. DRM issue consult requests (e.g., to OSE's drug use staff), as needed, for review of the REMS.
 - 4.1.3. Meet with the REMS Review Team to discuss the proposed REMS submission, including the REMS Document, REMS Materials, and REMS Assessment Plan.
 - 4.1.4. Prepare letter-ready comments for inclusion in the information request (IR).
 - 4.1.5. Participate in preparation for advisory committee meetings per established processes, if applicable.
- 4.2. The OSE SRPM will schedule team meetings for the REMS Review Team to discuss the proposed REMS submission, as needed.
- 4.3. The DRM TL and DRM Director or designee will clear the letter-ready comments.
- 4.4. The DRM RMA will send the cleared comments to the OND RPM and copy the OSE SRPM.

³⁵ Guidance for Review Staff and Industry: *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*.

³⁶ Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*.

- 4.5. OND RPM will send the cleared comments to the applicant.
- 4.6. The OND RPM will inform the REMS Review Team when the applicant submits their response to the comments.
- 4.7. The OND RPM will schedule teleconferences with the applicant at the request of the applicant or the REMS Review Team.
- 4.8. The DRM RMA will prepare the REMS Document and **REMS Attestations** concurrently for clearance.
- 4.9. The DRM QA analyst will send applicable REMS documents and REMS Attestations to ORP and OCC for clearance.
- 4.10. The DRM HCA will consult OPDP for review of REMS Materials and will incorporate their recommendations, as appropriate, into the review process.
- 4.11. The REMS Review Team will determine if REMS-related information should be included in the product labeling.³⁷
- 4.12. If the REMS Review Team finds the proposed REMS acceptable and the application is likely to be approved, the OND RPM will instruct the applicant to submit the final, agreed-upon REMS as an amendment to the application.
- 4.13. The REMS Review Team will discuss whether OCOMM should be consulted.

5. Prepare to Act on the Application

- 5.1. The DRM RMA will review the final, agreed-upon REMS submission to ensure that it is complete and acceptable, upload the DRM final primary review (with the rationale for the REMS, if applicable) in the CDER electronic document archiving system, and provide recommendations to the Marketing Application Review Team to incorporate the REMS Review Team's recommendations into the interdisciplinary review for the NDA or BLA.
- 5.2. The OND DDS/ADS will write the REMS memo after the DRM review is complete.
- 5.3. The OND RPM drafts the action letter:
 - 5.3.1. If the NDA/BLA is going to receive approval, the OND RPM will draft the appropriate REMS language for the approval letter, with DRM input on the REMS section. For REMS with ETASU, the OND SRPM sends the draft approval letter and the REMS memo to SRT for clearance. SRT will request clearance from OCC.
 - 5.3.2. If the NDA/BLA is going to receive a complete response (CR) for reasons other than the REMS, the OND RPM will draft the CR letter using templated REMS language.
 - 5.3.3. If the NDA/BLA is going to receive a CR and the REMS is one of the deficiencies, or if the letter will include an ETASU REMS notification,

³⁷ Most drug products with ETASU will include information about the ETASU in the product labeling. The Risk Management Analyst (RMA) should consult the OND Labeling Development Team for additional information.

the OND RPM will draft appropriate REMS language for the CR letter, with DRM input on the REMS section. For REMS with ETASU, the OND SRPM will send the draft CR letter and the REMS memo to SRT for clearance. SRT will request clearance from OCC.

- 5.4. The OND DDS/ADS will upload the cleared REMS memo in CDER's electronic document archiving system before, or at the time of, action on the application.
- 5.5. OND will act on the application in accordance with established procedures.³⁸
- 5.6. If the application is approved, the CDER electronic document archiving system will automatically notify ORP DIDP that the approval letter, along with the approved REMS Document and REMS Materials, issued.
- 5.7. ORP DIDP will redact the REMS-related documents and place the REMS Document and REMS Materials in an electronic folder for access by OCOMM DDI.
- 5.8. OCOMM DDI will post the REMS Document and REMS Materials on the FDA's REMS@FDA website within 3 days following approval.

6. Review of Resubmission of an Application

- 6.1. The OSE SRPM is notified³⁹ of the resubmission of an NDA/BLA.
- 6.2. The OSE SRPM will ensure that appropriate DRM staff (RMA and RMA TL) are added to the Marketing Application Review Team and included in all Marketing Application Review Team meetings, as appropriate (see Attachment 1).
- 6.3. DRM will review the REMS submission according to section A.4 of this MAPP.
- 6.4. The DRM RMA will review the final, agreed-upon REMS to ensure that the submission is complete and acceptable. They will upload the DRM final review, which includes the rationale for the REMS if the rationale was not documented in the first review cycle, in the CDER electronic document archiving system.
- 6.5. CDER staff will follow section A.5 of this MAPP for steps related to acting on an application that will require a REMS.

B. Postapproval REMS Determination and Review⁴⁰

1. Determining the Need for a REMS

³⁸ MAPP 6020.8 Rev. 1, *NDA/BLAs/Efficacy Supplements: Action Packages and Taking Regulatory Actions*.

³⁹ The OSE SRPM is notified via one of a variety of ways, including, but not limited to: electronic document room notifications, their CDER electronic document archiving system Inbox, administrative rounds, email from OND PM, etc.

⁴⁰ See footnote 4.

- 1.1. The ***Postapproval Safety Review Team*** will meet to discuss the evaluation of any safety signals for the drug product and the need for regulatory or other actions (e.g., a Drug Safety Communication), including the need for a REMS.
 - 1.1.1. If the Postapproval Safety Review Team determines that a REMS may be warranted, then the Project Manager^{41,42} will obtain the names of the appropriate staff to be part of the Postapproval Safety Review Team, including the DRM RMA and TL (see Attachment 1).
- 1.2. The Project Manager will schedule the Postapproval Safety Review Team meetings to discuss the need for a REMS.
- 1.3. The DRM RMA and TL will determine if any issues require input from the ROC.
- 1.4. A REMS Review Team, which may be a subset of the Postapproval Safety Review Team, will be established if the determination is made that consideration of a REMS is warranted.
- 1.5. The OSE SRPM will work with the appropriate OCD staff to schedule the ROC meeting.
 - 1.5.1. The OSE SRPM will schedule REMS Review Team meetings to prepare for the ROC meeting, if necessary.
 - 1.5.2. The REMS Review Team will attend the scheduled ROC meeting and present their proposal.
- 1.6. If the Postapproval Safety Review Team and REMS Review Team determines that a REMS:
 - 1.6.1. is not necessary, the DRM RMA will draft a review documenting the rationale for not requiring a REMS and upload the review in the CDER electronic document archiving system.⁴³
 - 1.6.2. is necessary, the DRM RMA will draft a review documenting the rationale for the proposed REMS and upload the review in the CDER electronic document archiving system.
- 1.7. The OND DDS/ADS will write the REMS memo after the DRM review is complete and is uploaded.
- 1.8. If a REMS is necessary, communication to the Applicant about the REMS requirements should occur as early as possible.
 - 1.8.1. The OND SRPM will draft the REMS Notification Letter and circulates to the REMS Review Team for input.

⁴¹ The project manager responsible for this task generally comes from the same office that is leading the evaluation of the safety signal.

⁴² MAPP 4121.3 *Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)*.

⁴³ The DRM RMA will draft a review of the rationale to not require a REMS if consideration of a REMS was discussed at a ROC, at a CD briefing, if the sponsor submitted a proposed REMS, and/or at the discretion of the DRM Division Director.

- 1.8.2. For REMS with ETASU, the OND SRPM sends the draft letter and REMS Memo to SRT for clearance. SRT will request clearance from OCC.
- 1.9. The OND DDS/ADS will upload the cleared REMS memo in CDER's electronic document archiving system.
- 1.10. The OND DDS/ADS signs the REMS Notification Letter to the applicant.
- 1.11. The OND SPRM sends an electronic courtesy copy of the REMS Notification Letter to the applicant.

2. Review of Proposed REMS

- 2.1. The OSE SRPM is notified⁴⁴ of the Prior Approval Supplement containing the proposed REMS submission.
- 2.2. DRM RMA, HCA, and RAA will initiate review of the proposed REMS⁴⁵ which includes one or more of the following activities in accordance with relevant goal dates:
 - 2.2.1. Ensure that the proposed REMS submission is complete (i.e., includes the REMS Document, REMS Materials, and REMS Supporting Document).
 - 2.2.2. Issue consult requests when necessary (e.g., to OSE's drug use staff) for review of the REMS.
 - 2.2.3. Meet with the REMS Review Team as needed to discuss the proposed REMS submission, including the REMS Document, REMS Materials, and REMS Assessment Plan.
 - 2.2.4. Prepare letter-ready comments for inclusion in an IR.
 - 2.2.5. Participate in preparation for advisory committee meetings per established processes, if applicable.
- 2.3. The OSE SRPM will schedule team meetings for the REMS Review Team to discuss the proposed REMS submission, as needed.
- 2.4. The DRM TL and DRM Director or designee will clear the letter-ready comments.
- 2.5. The DRM RMA will send the cleared comments to the OND SRPM and copy the OSE SRPM.
- 2.6. OND SRPM will send any comments to be communicated to the applicant.
- 2.7. The OND SRPM will inform the REMS Review Team when the applicant submits their response.
- 2.8. The OND SRPM will schedule teleconferences with the applicant at the request of the applicant or the REMS review team.
- 2.9. The DRM RMA will prepare the REMS Document and REMS Attestations concurrently for clearance.

⁴⁴ See footnote 25.

⁴⁵ Proposed REMS are submitted as a prior approval supplement.

- 2.10. DRM QA analyst will send applicable REMS Documents and REMS Attestations to ORP and OCC for clearance.
- 2.11. The DRM HCA will consult OPDP for review of REMS Materials and will incorporate their recommendations, as appropriate, into the review process.
- 2.12. The REMS Review Team will determine if REMS-related information should be included in the product labeling.
- 2.13. If the REMS Review Team finds the proposed REMS acceptable, the OND SRPM will instruct the applicant to submit the final, agreed-upon REMS as an amendment to the supplemental application.
- 2.14. The REMS Review Team will discuss whether OCOMM should be consulted.

3. Prepare to Act on the Final REMS Supplement

- 3.1. The DRM RMA will review the final, agreed-upon REMS submission, which is submitted as a prior approval supplement (PAS), to ensure that it is complete and acceptable. The DRM RMA will upload their final review in the CDER electronic document archiving system.
- 3.2. The OND SRPM will draft the action letter:
 - 3.2.1. If the PAS will receive approval, the OND SRPM will draft the appropriate REMS language for the approval letter with DRM input. For REMS with ETASU, the OND SRPM will send the draft approval letter to SRT for clearance. SRT will request clearance from OCC.
 - 3.2.2. If the PAS will receive a CR, the OND SRPM will draft the appropriate REMS language for the CR letter with DRM input. For REMS with ETASU, the OND SRPM will send the draft CR letter to SRT for clearance. SRT will request clearance from OCC.
- 3.3. OND will act on the PAS in accordance with established procedures.⁴⁶
- 3.4. If the PAS is approved, the CDER electronic document archiving system will automatically notify ORP DIDP that the approval letter, along with the approved REMS Document and the REMS Materials, issued.
- 3.5. ORP DIDP will redact the REMS-related documents and place the REMS Document and REMS Materials in an electronic folder for access by the OCOMM DDI.
- 3.6. The OCOMM DDI will post the REMS Document and REMS Materials on the FDA's REMS@FDA website within 3 days of approval.

REFERENCES

1. MAPP 6701.3 Development of a Single, Shared System (SSS) Risk Evaluation and Mitigation Strategy (REMS) or a Separate REMS with Elements to Assure

⁴⁶ MAPP 6020.8 Rev. 1, *NDA/BLAs/Efficacy Supplements: Action Packages and Taking Regulatory Actions*.

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- Safe Use (ETASU): Responsibilities and Procedures at <https://www.fda.gov/media/123900/download>
2. MAPP 4191.1 Risk Evaluation and Mitigation Strategies (REMS) Modifications and Revisions at <https://www.fda.gov/media/128782/download>
 3. Guidance for Industry: Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) at <https://www.fda.gov/media/79776/download>
 4. Guidance for Industry: Application of Statutory Factors in Determining When a REMS Is Necessary at <https://www.fda.gov/media/100307/download>
 5. MAPP 4151.8 Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions at <https://www.fda.gov/media/79353/download>
 6. MAPP 4151.1 Rev 1 Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain at <https://www.fda.gov/media/71608/download>
 7. Guidance for Review Staff and Industry: Best Practices for Communication Between IND Sponsors and FDA During Drug Development at <https://www.fda.gov/media/94850/download>
 8. Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products at <https://www.fda.gov/media/132157/download>
 9. MAPP 6020.8 Rev. 1, NDAs/BLAs/Efficacy Supplements: Action Packages and Taking Regulatory Actions at <https://www.fda.gov/media/72739/download>
 10. MAPP 4121.3 Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS) at <https://www.fda.gov/media/137475/download>
 11. MAPP 4520.1 Rev.2 Communicating Drug Approval Information <https://www.fda.gov/media/72544/download>
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DEFINITIONS

Action Letter. An action letter is issued to an applicant in response to the applicant's submission of an application or supplemental application to inform them of the final action taken on the application (e.g., FDA approval or complete response).

Filing Review Issues Identified letter. This letter informs an applicant of filing review issues or substantive review issues that were identified by the marketing application review team during the initial filing review of the application.

Letter-ready comments. Letter-ready comments are written comments that are formulated by the reviewer(s) of a submission and that are written sufficiently well (e.g.,

correct grammar, spelling, and punctuation) to be included in a communication (not always a letter) to the applicant.

Marketing Application Review Team. The members of the Marketing Application Review Team are the FDA subject matter experts who review an application when submitted. The team consists of reviewers and team leaders from OND, Clinical, Pharmacology-Toxicology, Biostatistics, Office of Pharmaceutical Quality, Clinical Pharmacology, Microbiology, and Virology; OND RPM; the Associate Director for Labeling (ADL); Office of Surveillance and Epidemiology (OSE) (may vary by application and meeting) and other offices as necessary.

Postapproval Safety Review Team. For the purpose of this MAPP, the Postapproval Safety Review Team consists of FDA experts who review safety data for marketed drug products, are involved in identifying, evaluating, and resolving newly identified safety signals (NISS), and/or responsible for reviewing other types of new safety information⁴⁷ for those drug products. Multiple offices in CDER, including the Office of Compliance (OC), Office of Generic Drugs (OGD), Office of New Drugs (OND), Office of Pharmaceutical Quality (OPQ), Office of Surveillance and Epidemiology (OSE), and Office of Translational Sciences (OTS) participate, depending on the office's role in CDER and the staff's expertise.

Pre- and Post- approval REMS Review Team (REMS Review Team). The REMS Review Team is a subset of the Marketing Application Review Team and the Postapproval Safety Review Team. The REMS Review team consists of staff from OSE's DRM (RMA, RMA TL, HCA, and RAA TL, and RAA), OSE's SRPM, OSE's , appropriate Division of Epidemiology and Division of Pharmacovigilance, OND (the clinical reviewer, CDTL, DDS/ADS, and OND SRPM), CDER's Office of Compliance, and other CDER staff as needed (e.g., CSS, and Pediatric and Maternal Staff).

Proposed-REMS Submission. Applies to proposed REMS voluntarily submitted by the applicant and those submitted in response to the Agency's communication to the applicant of the REMS requirements. A proposed REMS submission includes 2 parts: (1) the proposed REMS, which includes the proposed REMS Document and proposed REMS Materials and (2) the proposed REMS Supporting Document.

REMS Assessment Plan. A REMS Assessment Plan describes how the applicant intends to assess the performance of the REMS in meeting its risk mitigation goals and objectives. The REMS Assessment Plan is outlined in the REMS approval letter for NDAs and BLAs and described in detail in the REMS Supporting Document.⁴⁸

⁴⁷ Section 505-1(b)(c) of the FD&C Act.

⁴⁸ Draft Guidance for Industry: *REMS Assessment: Planning and Reporting*. When final, this guidance will represent the FDA's current thinking on this topic.

REMS Attestations. REMS Attestations are the statements outlining the required activities that REMS participants (e.g., prescribers, pharmacies, and patients) agree to carry out when enrolling in the REMS. Attestations may be included in a variety of forms.

REMS Document. This document establishes the goals and requirements of the REMS as they relate to the required REMS elements.

REMS Element Retraction-Addition Letter. This letter informs an applicant that the entire REMS requirement is being retracted, that one or more required REMS elements are being removed, or that new REMS elements are being added. This letter is sent after a REMS Notification Letter, REMS Modification Notification or Complete Response letter has been sent but before the new REMS or REMS modification has been approved.

REMS Materials. REMS Materials are the documents that participants use to comply with a REMS requirement, such as enrollment forms or educational materials.

REMS Memorandum (REMS Memo). A REMS Memo documents OND and OSE's joint decision on the need for a REMS and describes the content of the REMS after consideration of the statutory factors. For postapproval REMS, the REMS Memo describes the "new safety information" that led to the REMS requirement. The REMS Memo is uploaded in CDER electronic document archiving system prior to action taken on a new or supplemental submission.

REMS Notification Letter. The REMS Notification Letter informs an applicant that FDA has determined that a REMS is necessary to ensure the benefits outweigh the risks of the drug product. The letter also includes the elements of the REMS, the content of the proposed REMS submission, and the timeline for when the proposed REMS must be submitted.

REMS Supporting Document. This document expands on information in the REMS Document by providing additional information about the REMS, such as the rationale for requiring a REMS and supporting information about the design, implementation, and assessment of the REMS. This document may also cover topics such as implementation processes, compliance and enforcement policies and procedures, definitions, knowledge assessment scoring criteria, or the REMS assessment plan. For example, a REMS Supporting Document may describe why a REMS is necessary (based on application of the statutory factors) or how the REMS ensures that the benefits of the drug outweigh the risks.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions

ATTACHMENT 1: When to Include DRM in Meetings**A. DRM should be included as a member of the Marketing Application Review Team in the circumstances listed below.**

For original NDA/BLA submissions, include the appropriate DRM staff when:

- The drug product is a new molecular entity, regardless of whether a proposed REMS is included in the application.
- The applicant submits a proposed REMS with the application.
- The drug product will be part of a class of drugs that already has a REMS.
- An advisory committee meeting is planned to discuss safety-related issues.
- A previously unidentified safety signal arises at any time during the review of the submission.

For efficacy supplements and 505(b)(2) submissions, include the appropriate DRM staff when:

- A safety signal that may result in a boxed warning is identified prior to application submission, at the pre-NDA/BLA phase, or after submission at either the Benefit-Risk Scoping Meeting or a Joint Assessment Meeting.
- The applicant proposes a boxed warning.
- The efficacy supplement is submitted based on the results of a postmarketing study or clinical trial that is the basis for the proposal to change the indication to a second line treatment, to add a limitation of use, or make other safety-related changes.
- The efficacy supplement or 505(b)(2) application is submitted with a risk management program with restrictive elements.
- The drug product re-entered the market after removal due to safety reasons.
- An advisory committee meeting is planned to discuss safety-related issues or benefit-risk balance for a new indication.
- A previously unidentified safety signal arises at any time during the review of the submission.
- The applicant submits a proposed REMS with the submission.
- The drug product has been or will be part of a class of drugs that already has a REMS.

B. DRM should be included as a member of the Postapproval Safety Review Team in the circumstances listed below.

- A safety signal that may result in a boxed warning is identified.
- The applicant proposes a boxed warning.
- An efficacy supplement is submitted to change the indication to a second line treatment, or to add a limitation of use, or other safety-related changes in response to a safety-related PMR, other postmarketing studies, or clinical trials that the applicant has conducted or become aware of.

- The efficacy supplement or 505(b)(2) application is submitted with a risk management program with restrictive elements.
- The drug product re-entered the market after the product was removed from the market due to safety reasons.
- An advisory committee meeting is planned to discuss safety-related issues.
- A previously unidentified safety signal arises at any time during the review of the submission.
- A signal arises, and there is early consideration of the need for a REMS for a drug product that is the subject of an approved NDA, BLA, or ANDA.