POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

Risk Evaluation and Mitigation Strategy (REMS) Assessment

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PURPOSE

This MAPP describes the policies, responsibilities, and procedures to be used in the Center for Drug Evaluation and Research (CDER) for the review of ***risk evaluation and mitigation strategy (REMS) Assessment Reports***[1] submitted to the Agency according to the timetable for submission of assessments or another required timeframe for submission.

This MAPP does not address policies, responsibilities, and procedures for review of REMS assessments that are required to be submitted as part of an efficacy supplement.

BACKGROUND

Section 505-1 of the Federal Food, Drug and Cosmetic Act (FD&C Act), as added by the Food and Drug Administration Amendments Act of 2007 (FDAAA) and later amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA),

[1] Terms that appear in ***bold italic*** type upon first use are defined on page 10.

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 outweigh its risks.[2, 3, 4]

A REMS may include a Medication Guide (MG), a patient package insert, a communication plan, and/or packaging and disposal requirements.[5] FDA also may require certain elements to assure safe use (ETASU) as part of a REMS for a drug or biologic.[6] In addition, a proposed REMS for a new drug application (NDA) and biologic license application (BLA) must have a timetable for submission of assessments,[7] that

- Includes assessments submitted to the FDA by the dates that are 18 months, 3 years after the strategy is initially approved and in the 7th year after the strategy is approved, or
- is at a frequency specified in the REMS and can be increased or reduced in frequency under certain circumstances or eliminated under certain circumstances.

With limited exceptions, REMS assessments are also required when submitting a supplemental application for a new indication for use, when required by the strategy, or whenever FDA determines that an assessment is needed to evaluate whether the strategy should be modified to ensure the benefits of the drug outweigh the risks, or to minimize the burden on the healthcare delivery system of complying with the strategy.[8] In addition to the required assessments, an applicant may voluntarily submit an assessment of an approved REMS at any time.[9]

Section 505-1(g)(3) of the FD&C Act specifies that a REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified. The statute does not specifically describe how this assessment is to be conducted; however, two draft guidances for industry are available for this purpose.[10]

[2] Public Law 110-85, September 27, 2007, available at https://www.govinfo.gov/content/pkg/PLAW-110publ85/html/PLAW-110publ85.htm, accessed February 14, 2019.
[3] Public Law 112-144, July 9, 2012, available at https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf accessed February 14, 2019.
[4] See Section 505-1(a) of the FD&C Act.
[5] Sections 505-1(e)(2)-(4) of the FD&C Act.

[6] See Section 505-1(f)(1) of the FD&C Act.

[7] See Section 505-1(c)-(d) of the FD&C Act.

[8] See Section 505-1(g)(2) of the FD&C Act.
[9] See Section 505-1(g)(1) of the FD&C Act.
[10] For more information on how to conduct a REMS assessment, please see the draft guidances for industry, *REMS Assessment: Planning and Reporting* (January 2019) and *Survey Methodologies to Assess REMS Goals that Relate to Knowledge* (January 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

POLICY

- The Office of Surveillance and Epidemiology (OSE) Division of Risk Management (DRM) staff will lead a ***CDER Multidisciplinary REMS Assessment Review Team*** ("REMS Assessment Review Team") including representatives from other OSE divisions, Office of New Drugs (OND), Office of Generic Drugs (OGD), Office of Compliance (OC), and other CDER offices as relevant, in the review of the ***REMS Assessment Report***.

- The OSE Safety Regulatory Project Manager (SRPM) will serve as ***the point of contact (POC)*** for communication with the ***Industry Working Group*** (IWG) POC for REMS Assessment Reports of ***shared system REMS*** **(**including ***single shared system REMS*****),** or with the abbreviated new drug application (ANDA) applicant /ANDA IWG POC for a ***separate REMS***.

- The OND Safety Regulatory Project Manager (SRPM)/ Regulatory Project Manager (RPM) will serve as the POC for communications with NDA and BLA applicants.

- The REMS Assessment Review Team will discuss issues regarding the REMS Assessment Report with the ***REMS Oversight Committee (ROC),*** as necessary.[11]

- The REMS Assessment Review Team will conduct its review of REMS Assessment Reports in accordance with CDER's policies on equal voice[12] and, if necessary, dispute resolution.[13]

- If the REMS Assessment Review Team determines that a REMS modification to change the goal of the REMS or add or remove an element is necessary following the review of a REMS Assessment Report, a ***REMS Memorandum (Memo)*** will be written and signed prior to or at the time the ***REMS Modification Notification L****etter* is issued[14].

[11] CDER's REMS Oversight Committee (ROC) provides CDER senior leadership advice on staff recommendations for applications-specific REMS issues.
[12] MAPP 4151.8, Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions.
[13] MAPP 4151.1 Rev.1, Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain, and MAPP 4151.2Rev. 1 Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director
[14] MAPP 4191.1, Risk Evaluation and Mitigation Strategies Modifications and Revisions

RESPONSIBILITIES

The following CDER offices are part of the REMS Assessment Review Team: OSE, OND, OC, and OGD. The following CDER Offices may also be included:

- The Office of Medical Policy's (OMP's) Patient Labeling Team (PLT) if a Medication Guide (MG) is a component of the REMS
- The OND Division of Pediatric and Maternal Health (DPMH) for all REMS that address teratogenicity or embryofetal toxicity
- Other offices including the Office of Translational Science (OTS)/Office of Biostatistics, Office of Regulatory Policy (ORP) and the Office of Chief Counsel (OCC) may be included if additional expertise is needed

OSE DRM REMS Assessment Analyst (RAA)

- Serves as the REMS assessment subject matter expert (SME) on the REMS Assessment Review Team
- Co-chairs, with the OSE SRPM, the REMS Assessment Review Team meetings
- Reviews the REMS Assessment Report submissions and provides content expertise
- Confers with the DRM REMS Assessment Team Leader to determine if any information requests or additional consultations (consults) to other OSE divisions or CDER offices are necessary to complete the review
- Writes and archives the REMS Assessment Review incorporating the input of the REMS Assessment Review Team

OSE DRM REMS Assessment Team Leader (ATL)

- Works with the RAA to ensure timely review of the REMS Assessment Report
- Identifies, with input from the REMS Assessment Review Team, DRM Management and other offices, the need to discuss the REMS Assessment Report with the ROC
- Informs the REMS Assessment Review Team about progress on reviewing the REMS Assessment Report and whether there are issues that may impact the review timeline
- Identifies subject matter expertise that should be consulted

OSE Chief Project Management Staff (CPMS)

- Notifies the assigned OSE SRPM when a REMS Assessment Report is submitted to the Agency via CDER's electronic document archival system's Inbox.

OSE Safety Regulatory Project Manager (SRPM)

- Schedules REMS Assessment Review Team meetings
- Co-chairs REMS Assessment Review Team meetings with the RAA
- Communicates with the POC for the IWG for a shared system REMS or the **ANDA applicant/ANDA IWG POC** for the separate REMS during the review of the REMS Assessment Report

- Prepares and submits meeting requests to the ROC to discuss the REMS Assessment Report, as needed

OND Safety Regulatory Project Manager (SRPM)/Regulatory Project Manager (RPM)

- Drafts and initiates clearance of the appropriate REMS Assessment Letter and issues the letter to NDA/BLA applicant(s).

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

- Oversees the management and coordination of OND review division activities regarding the review of the REMS Assessment Report
- Writes and archives a REMS memo when appropriate
- Serves as the signatory for REMS Assessment Letters issued to NDA or BLA applicants for REMS, including shared system REMS

OC REMS Compliance Team

- Oversees the management and coordination of OC activities regarding the review of the REMS Assessment Report. Tracks receipt of REMS Assessment Reports from applicants and notifies DRM, OND SRPM/RPM, and OGD Office of Bioequivalence REMS Coordinator, of REMS Assessment Report submissions that are due within 30 calendar days or are overdue
- Reviews REMS Assessment Report for compliance with timeliness of submission and submission of all metrics in the assessment plan
    - Uploads review into the CDER electronic document archiving system, and ensures that DRM, OND SRPM/RPM, OSE SRPM, and OGD REMS Coordinator, as appropriate, are notified of entry

OGD Office of Bioequivalence Director or Designee

- Serves as the signatory for REMS Assessment Letters issued to ANDA applicants for a separate REMS
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OGD Office of Bioequivalence REMS Coordinator

- Oversees the management and coordination of OGD activities regarding the review of the REMS Assessment Report
- Drafts, and initiates clearance of REMS Assessment Letters issued to ANDA applicants with a separate REMS after the completion of the REMS Assessment Review

REMS Assessment Review Team

- Reviews meeting materials and attends REMS Assessment Review Team meetings

- Prepares discipline review within the timeframe outlined in the consult request, if applicable[15]

PROCEDURES

Overview

The REMS Assessment Review process starts when OSE receives notification of a REMS Assessment Report submission from the document room. The OSE DRM leads the REMS Assessment Review and convenes a REMS Review Assessment Team comprised of CDER subject matter experts as appropriate for the review of the report. The review of a REMS Assessment Report is complete when the DRM RAA archives the final DRM REMS Assessment Review in the CDER electronic document archival system, and the appropriate REMS Assessment Letter has been issued to the applicant(s). The timeline for completion of a REMS Assessment Review by DRM and issuance of the appropriate REMS Assessment Letter, except in certain circumstances[16], is no later than 180 calendar days from receipt of the REMS Assessment Report submission.

1. Initiation of REMS Assessment Report Review

1.1. The OSE Chief Project Management Staff will notify the assigned OSE SRPM when a REMS Assessment Report is submitted to the Agency via CDER's electronic document archival system's Inbox.

1.2. The OSE SRPM assigns coordination of review to the DRM ATL.

1.3. The DRM ATL triages the REMS Assessment Report to determine whether it appears complete and acceptable for review.

1.3.1. If the report is not acceptable for review the DRM ATL drafts language for the ***REMS Assessment Incomplete-Additional Information Required Letter*** and sends the letter to the OND SRPM or the OGD Office of Bioequivalence as appropriate.

1.3.2. If the REMS Assessment Report is determined to be acceptable for review, the DRM ATL will inform the OSE SRPM on 1) the number and timing of REMS Assessment Review Team meetings, 2) a list of meeting participants for the REMS Assessment Review Team meetings, and 3) information regarding any additional review assignments or other office or division consults needed (e.g., Division of Epidemiology, Office of Biostatistics).

1.4. The DRM ATL assigns the RAA and other relevant DRM staff.

1.5. The OSE SRPM sends consults as necessary and schedules the REMS Assessment Review Team Meetings.

[15] If applicable, the Division of Epidemiology Drug Use Analyst must ensure vendor clearance for any proprietary drug utilization information that will be included in the final REMS Assessment Review.

[16] Exceptions to this timeline may be made in cases where the REMS Assessment Report is lengthy, when the review requires consultation with other offices or divisions, or when responses to information requests are not received in time to complete the review in 180 calendar days.

2. Review of REMS Assessment Report

2.1. The DRM RAA reviews the REMS Assessment Report. To complete the review the DRM RAA may perform one or more of the following activities:

2.1.1. Drafts an information request (IR) if additional information is necessary to complete the review

2.1.1.1. Obtains ATL approval of IR language and sends IR to the applicant(s) through the OND SRPM/RPM if it involves an individual NDA/BLA product REMS or through the OSE SRPM for shared system REMS or a separate REMS.

2.1.1.2. If the applicant(s) do not provide the data after an IR is sent, the DRM RAA will draft language for the REMS Assessment Incomplete-Additional Information Required letter and send it to the OND SRPM/RPM or the OGD Office of Bioequivalence as appropriate following clearance by the DRM ATL.

2.1.2. Consults with other DRM staff and/or the OND DDS/ADS regarding other REMS review activities (e.g., pending supplements, including REMS modifications).

2.1.3. Drafts DRM REMS Assessment Review and meeting slides and incorporates key report findings, preliminary conclusions received from the consulted offices[17], and recommendations for discussion at REMS Assessment Review Team meetings after clearance by DRM ATL.

2.1.4. Identify specific issues that need discussion or input from the ROC.

2.2. The consulted divisions or offices conduct a review of assigned portions of the REMS Assessment Report, which includes one or more of the following activities:

2.2.1. Draft interim comments or language for an IR, if necessary.

2.2.2. Prepares draft review and/or slides, if applicable, with key report findings, preliminary conclusions, and recommendations for discussion at REMS Assessment Review Team meetings.

2.3. The OSE SRPM distributes the slides and draft reviews to the REMS Assessment Review Team prior to the meeting.

3. Discussion of review findings with REMS Assessment Review Team

3.1. The RAA and other consulted staff present key review findings, preliminary conclusions, and recommendations at the scheduled REMS Assessment Review Team meetings.

3.2. The REMS Assessment Review Team discusses the findings, conclusions, recommendations, and next steps including determining one or more of the following:

3.2.1. the REMS Assessment Report is complete

3.2.2. the REMS is meeting its risk mitigation goals

[17] Preliminary conclusions include whether the Assessment report is complete, whether the REMS is meeting its goals, and whether the REMS requires modification based upon the REMS assessment report findings.

3.2.3. the REMS requires modification based upon the REMS Assessment Report findings

3.2.4. the REMS assessment plan requires revisions

3.2.5. the REMS Assessment Report findings should be discussed at a Drug Safety and Risk Management Advisory Committee or another advisory committee.[18]

3.3. The OSE SRPM will work with the appropriate Office of the Center Director (OCD) staff to schedule the ROC meeting, if needed.

3.3.1. The OSE SRPM will schedule additional REMS Assessment Review Team meetings to prepare for the ROC meeting, if necessary.

3.3.2. The REMS Assessment Review Team will attend the scheduled ROC meeting and present their proposal.

3.4. The RAA incorporates the discussion, recommendations, and conclusions into the DRM REMS Assessment Review.

4. Completion of REMS Assessment Review

4.1. The DRM director or designee clears the final DRM REMS Assessment Review.

4.2. The OND DDS/ADS reviews the final DRM REMS Assessment Review and provides comments or concurrence with the review.

4.3. The DRM RAA uploads the final review into the CDER electronic document archiving system, and ensures that the OND SRPM/RPM, OSE SRPM, and OGD REMS Coordinator, as appropriate, are notified of entry.

5. Communication of Conclusions and Comments to Applicant(s)

5.1. The OND SRPM/RPM or OGD REMS Coordinator[19] drafts language for the appropriate REMS Assessment Letter.

5.1.1. Letters that include REMS Modification Notification, and the REMS memo (if applicable) are sent to the Safety Requirements Team and OCC for clearance prior to being sent to the DRM RAA, DRM ATL, and Director or designee (see 5.3)

5.2. The DRM RAA, DRM ATL, and Director or designee review the language for the appropriate REMS Assessment Letter.

5.3. The OND DDS/ADS clears and signs the appropriate REMS Assessment Letter to be issued to for NDA, BLA applicants for REMS, including shared system REMS.

5.4. The OGD Office of Bioequivalence Director or designee, as appropriate, clears and signs the appropriate REMS Assessment Letter for ANDA applicant(s) for separate REMS.

[18] Section 505-1(f)(5) of the FD&C Act.

[19] The OGD REMS Coordinator only drafts language for a REMS Assessment letter to ANDA applicant(s) in a separate REMS that does not include NDAs.

REFERENCES

1. Draft Guidance for Industry: REMS Assessment: Planning and Reporting https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rems-assessment-planning-and-reporting
2. Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge https://www.fda.gov/regulatory-information/search-fda-guidance-documents/survey-methodologies-assess-rems-goals-relate-knowledge
3. MAPP 4151.8 Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions https://www.fda.gov/media/79353/download
4. MAPP 4151.1 Rev 1 Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain https://www.fda.gov/media/71608/download
5. Draft Guidance for Industry: Development of a Shared System REMS https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-shared-system-rems-guidance-industry
6. Draft Guidance for Industry: Waivers of the Single, Shared System REMS Requirement https://www.fda.gov/regulatory-information/search-fda-guidance-documents/waivers-single-shared-system-rems-requirement-draft-guidance-industry
7. Draft Guidance for Industry: Use of a Drug Master File for Shared System REMS Submissions https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-drug-master-file-shared-system-rems-submissions-guidance-industry

DEFINITIONS

ANDA Applicant/ANDA IWG - refers to a single ANDA applicant that develops and implements a REMS (ANDA Applicant), or to the working group that more than one ANDA applicants have formed to develop and implement a separate REMS (ANDA IWG).

CDER Multidisciplinary REMS Assessment Review Team – consists of the following individuals (at a minimum): DRM RAA and TL, Risk Management Analyst (RMA) and TL, OSE SRPM, OND DDS/ADS and OND SRPM/RPM, OC REMS Compliance Team, and OGD REMS Coordinator.

DRM REMS Assessment Review- The DRM REMS Assessment Review documents the findings, conclusions and recommendations from the CDER Multidisciplinary REMS Assessment Review Team on the review of a REMS Assessment Report.

Industry Working Group (IWG) – refers to the working group that the applicants have formed to develop and implement a shared system REMS.

Point of Contact (POC) – the designated person within the IWG that the OSE SRPM communicates with regarding the development of the SSS or separate REMS. This POC will facilitate communication between the Agency and the IWG.

REMS Assessment Letters

> **REMS Assessment Acknowledgement Letter –**communicates the findings, conclusions, and recommendations from the FDA review of the REMS Assessment to the REMS application holder. May also include REMS Assessment Plan Revision and a REMS Modification Notification
>
> **REMS Assessment Incomplete – Additional Information Required Letter –** communicates that the information in the report is insufficient to complete a review of the REMS assessment report.

REMS Assessment Report - The document submitted by applicants that contains information generated from the analysis of the metrics outlined in the REMS Assessment Plan.

REMS Memorandum (REMS Memo) - A memo to the file to document that OND and OSE jointly decided on the need for a REMS and the content of the REMS, after consideration of statutory factors. For post-approval REMS and REMS modifications that change the goal or add or remove an element, the REMS Memo describes the "new safety information" that led to the REMS requirement. The REMS Memo is archived in CDER's electronic document tracking and archiving system prior to action taken on a new or supplemental submission.

REMS Modification Notification Letter – communicates the need for and rationale for a REMS modification, as well as any specific changes to the REMS goals or requirements; may be issued with REMS assessment acknowledgement letter or separately.

REMS Oversight Committee (ROC) – a committee comprised of CDER senior leadership that provides advice on staff recommendations for application-specific REMS issues in order to establish a consistent approach to CDER's decision-making related to requiring ETASU REMS and design, implementation, and assessment of REMS.

Separate REMS [*for the purposes of this document*] – an approved separate, shared system REMS for an ANDA applicant/ANDA IWG that was granted a waiver from the single, shared system REMS requirement with the reference listed drug (RLD). The separate REMS must use an aspect of the ETASU that is comparable to that of the NDA RLD REMS and achieve the same level of safety.

Shared System REMS – A REMS that encompasses multiple prescription drug products and is developed and implemented jointly by two or more applicants.

Single, Shared System (SSS) REMS - REMS that include ETASU and at least one ANDA product and its RLD. The requirement under section 505-1(i)(1)(B) regarding a SSS REMS only applies to ANDAs.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions