POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

Review of Proposed Methodological Approaches to Assess a Risk Evaluation and Mitigation Strategy (REMS)

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PURPOSE

This MAPP describes the policies, responsibilities, and procedures Center for Drug Evaluation and Research (CDER) staff will follow for the review of methodological approaches that are proposed by applicants to assess a risk evaluation and mitigation strategy (REMS), also referred to in this document as a ***REMS Assessment Methodology***[1].

This MAPP does not address policies, responsibilities, or procedures for review of **REMS Assessments Reports** submitted to the Agency according to the timetable for submission of assessments.

BACKGROUND

Section 505-1 of the Federal Food, Drug and Cosmetic Act (FD&C Act) 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.

[1] Terms that appear in ***bold italic*** type upon first use are defined on page 11.

A REMS may include a Medication Guide (MG), a patient package insert, a communication plan, and/or packaging and disposal requirements.[2] FDA also may require certain elements to assure safe use (ETASU) as part of a REMS for a drug or biologic.[3] In addition, a REMS for a new drug application (NDA) or biologics license application (BLA) must have a timetable for submission of assessments[4] that:

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

REMS assessments may also be required when applicants submit a supplemental application for a new indication for use, when required by the REMS, or whenever FDA determines that an assessment is needed to evaluate whether the approved REMS 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 REMS.[5] In addition to the required assessments, an applicant may voluntarily submit an assessment of an approved REMS at any time.[6]

Section 505-1(g)(3) of the FD&C Act specifies that a REMS assessment shall include, with respect to each goal in the REMS, an assessment of the extent to which the approved REMS, 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, FDA has issued draft guidance for industry which, when finalized, will provide the Agency's thinking for this purpose.[7]

A variety of methodological approaches may be used to support an assessment of a REMS program to evaluate knowledge, safe use behaviors, patient outcomes, and compliance with REMS requirements. Examples of approaches that applicants may employ include surveys; drug use, claims-based, or observational studies; and non-compliance and audit plans.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends that applicants obtain FDA feedback on the details of the methodological approaches,

[2] Sections 505-1(e)(2)-(4) of the FD&C Act.

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

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

[5] See Section 505-1(g)(2) of the FD&C Act.

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

[7] For the guidances related to REMS assessments, see the References section.

study protocols, other analysis plans and assessment approaches used to assess a REMS program before implementing them.

POLICY

- The Office of Surveillance and Epidemiology (OSE) Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) staff will lead the review of proposed methodological approaches submitted by applicants to assess a REMS.

- The OSE Safety Regulatory Project Manager (SRPM) will serve as the point of contact (POC) for communications with applicants for REMS Assessment Methodology submissions.[8]

- CDER conducts its review of a REMS Assessment Methodology in accordance with CDER's policies on equal voice and, if necessary, dispute resolution.[9]

- CDER retains records related to the review of REMS Assessment Methodologies within the ***CDER Electronic Records Keeping Systems (ERKS)*** as applicable.[10]

- CDER issues a ***REMS Assessment Methodology Acknowledgement Letter*** to notify the applicant the submission is received and of the goal date for completion of the review.

- CDER completes its review of the REMS Assessment Methodology and issues a ***REMS Assessment Methodology General Advice Letter*** to convey the recommendations/comments within 90 calendar days from receipt of the REMS

[8] The OSE SRPM also serves as POC for communications with the Industry Working Group (IWG) for a shared system REMS.
[9] For more information on equal voice, see MAPP 4151.8 Rev. 1, *Equal Voice: Collaboration and Regulatory and Policy Decision-Making* in CDER. Available at: https://www.fda.gov/media/157807/download.
[10] For more information on managing and retaining records, see MAPP 7600.11, *CDER Electronic Record Keeping Systems* (available at: https://www.fda.gov/media/89742/download) and the FDA Staff Manual Guide (SMG) 3291.1, *FDA Records Management Policy* (available at: https://www.fda.gov/media/81394/download).

Assessment Methodology submission. Issuance of this letter closes the 90-day goal date.[11,12,13]

- CDER issues a ***REMS Assessment Methodology Incomplete Letter*** if the submission is missing information necessary for the review. Issuance of this letter closes the 90-day goal date.

- CDER issues a ***REMS Assessment Methodology Withdrawal Letter*** to notify the applicant that CDER considers its submission withdrawn. Issuance of this letter closes the 90-day goal date. Reasons to withdraw a submission include but are not limited to the following:
    - An applicant's response to an information request (IR) includes additional information outside the scope of the initial IR that would require additional time to review (e.g., the IR response contains additional questions, unsolicited revisions to the methodology, or amends the original submission with new information)
    - An applicant's proposed start date to use the REMS Assessment Methodology in a REMS assessment is within 90 days of submission.

- CDER issues a ***REMS Assessment Methodology Acknowledge Withdrawal Letter*** to acknowledge an applicant's request to withdraw its submission[14].

RESPONSIBILITIES

DMAMES is the lead in the review of a REMS Assessment Methodology and, when additional subject matter expertise is needed, will collaborate with or obtain input from other groups, including but not limited to other OSE Divisions; the Office of New Drugs (OND) Review Division; Office of Generic Drugs (OGD)/Office of Safety and Clinical Evaluation (OSCE); and the Office of Translational Sciences (OTS)/Office of Biostatistics (OB).

OSE DMAMES REMS Assessment Analyst (RAA)

- Serves as the REMS assessment subject matter expert (SME).
- Triages and reviews the proposed REMS Assessment Methodology and provides content expertise.

[11] The reauthorization of the Prescription Drug User Fee Act (PDUFA VII) established performance goals for review of REMS assessment methods and study protocols used to assess a REMS program within 90 days of receipt for NDAs and BLAs.
[12] Submissions only containing REMS Assessment Methodologies will be reviewed within 90 days. The 90-day goal date will not apply to REMS Assessment Methodologies included in other submissions.
[13] The performance goal to review within 90 days does not apply to ANDA REMS Assessment Methodology submissions. CDER will follow the same process described in this document for the review of ANDA REMS Assessment Methodology submissions.
[14] The receipt of an applicant's submission to withdraw a previously submitted REMS Assessment Methodology submission closes the 90-day goal date.

- Confers with the DMAMES REMS Assessment Team Leader to determine if any:
  - IRs are necessary to complete the review and/or
  - additional SMEs from other OSE divisions or CDER offices are necessary to complete the review.
- Identifies the need for and participates in REMS Assessment Methodology meetings.
- Drafts and archives the REMS Assessment Methodology Review incorporating the input from other SMEs, if applicable.

OSE DMAMES REMS Assessment Team Leader (ATL)

- Works with the RAA to ensure timely review of the REMS Assessment Methodology.
- Identifies, in collaboration with the RAA, SMEs who should be consulted for the review.
- Identifies the need for and participates in REMS Assessment Methodology meetings.

OSE DMAMES Director or Designee

- Serves as the signatory for REMS Assessment Methodology Reviews and REMS Assessment Methodology Letters.
- Participates in REMS Assessment Methodology meetings as needed.
- Seeks alignment with the OND Deputy Director for Safety (DDS)/Associate Director for Safety (ADS) and other SMEs on the recommendation(s) in the REMS Assessment Methodology Review.

OSE Chief Project Management Staff (CPMS)

- Triages and assigns an OSE SRPM when a REMS Assessment Methodology and other submission(s) associated with the REMS Assessment Methodology are submitted to the Agency.
- Ensures that REMS Assessment Methodology submissions are accurately coded in the CDER ERKS as part of the triaging responsibility, and submits change requests, as appropriate.

OSE Safety Regulatory Project Manager (SRPM)

- Issues collaboration request to SMEs, such as Office of Pharmacovigilance and Epidemiology (OPE) and OTS, if applicable.
- Makes OND DDS/ADS and OND SRPM/ORO RPM aware of the REMS Assessment Methodology submission.
- Issues IRs to applicants.[15]
- Serves as the POC for communications with applicants for the REMS Assessment Methodology.

[15] The OSE SRPM will issue IRs to the industry working group POC for any shared system REMS.

- Ensures that REMS Assessment Methodology submissions are accurately coded in the CDER ERKS during review of the submission, and submits change requests, as appropriate.
- Schedules REMS Assessment Methodology meetings, as needed.
- Drafts, coordinates clearance of, and issues the appropriate REMS Assessment Methodology Letters to applicants.

OSE Office of Pharmacovigilance and Epidemiology (OPE) Subject Matter Experts

- Review and reply to consult requests for epidemiologic, pharmacovigilance, and drug utilization subject matter expertise as needed.
- Participate in drafting IRs, as applicable.
- Participate in REMS Assessment Methodology meetings as needed.

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

- Provides input for clinical subject matter expertise as needed.
- Provides input and seeks alignment with the DMAMES director and other SMEs on the recommendation(s) in the REMS Assessment Methodology Review.
- Participates in REMS Assessment Methodology meetings as needed.
- Reviews DMAMES recommendations that will be included in a *REMS Assessment Methodology General Advice Letter.*

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

- Notifies the OSE SRPM when a submission contains a REMS Assessment Methodology and is not coded accurately in the CDER ERKS.

OTS Office of Biostatistics (OB) Subject Matter Experts

- Review and reply to consult requests for statistical subject matter expertise as needed.
- Participate in drafting IRs, as applicable.
- Participate in REMS Assessment Methodology meetings as needed.

OGD Office of Safety and Clinical Evaluation (OSCE) REMS Coordinator

- Notifies the OSE SRPM when a submission contains a REMS Assessment Methodology and is not coded accurately in the CDER ERKS.

PROCEDURES

1. Receipt and Triage of REMS Methodology Submission

1.1. The OSE CPMS receives notification of receipt of the REMS Assessment Methodology from the CDER ***Electronic Information System (EIS)*** or ERKS.

1.2. The OSE CPMS assigns the OSE SRPM.

1.3. The OSE SRPM assigns the applicable DMAMES ATL via the CDER EIS.

1.4. The DMAMES ATL assigns the DMAMES RAA.
1.5. The DMAMES RAA triages the REMS Assessment Methodology submission to determine whether it appears to be missing information necessary for review[16] and whether the proposed start time to use the REMS Assessment Methodology in a REMS assessment is within 90 days of submission.
  1.5.1. If the REMS Assessment Methodology submission is missing information necessary for review, the DMAMES RAA and ATL draft language for the *REMS Assessment Methodology Incomplete Letter* and communicate the language to the OSE SRPM through the CDER EIS.
    1.5.1.1. The OSE SRPM drafts, obtains clearance, and uploads the *REMS Assessment Methodology Incomplete Letter* to the CDER EIS.
    1.5.1.2. The DMAMES Director or designee clears and signs the *REMS Assessment Methodology Incomplete Letter* in the CDER EIS.
  1.5.2. If the Applicant's proposed start date to use the REMS Assessment Methodology in a REMS assessment is within 90 days of submission, the DMAMES RAA and ATL draft language for the *REMS Assessment Methodology Withdrawal Letter* and communicate the language to the OSE SRPM through the CDER EIS.
    1.5.2.1. The OSE SRPM drafts, obtains clearance, and uploads the *REMS Assessment Methodology Withdrawal Letter* to the CDER EIS
    1.5.2.2. The DMAMES Director or designee clears and signs the *REMS Assessment Methodology Withdrawal Letter* in the CDER EIS.
1.6. If the REMS Assessment Methodology submission is not missing information and the start date to use the REMS Assessment Methodology in a REMS assessment is not within 90 days of submission, the DMAMES RAA will inform the OSE SRPM that the submission is acceptable for review through the CDER EIS.
  1.6.1. The OSE SRPM drafts, obtains clearance of, and signs the *REMS Assessment Methodology Acknowledgement Letter* in the CDER EIS.
1.7. The DMAMES ATL and RAA determine if additional SMEs are needed for the review of the REMS Assessment Methodology submission.
  1.7.1. If additional SMEs are needed, the DMAMES ATL or RAA informs the OSE SRPM through the CDER EIS.
1.8. The OSE SRPM issues collaboration requests to the SMEs.
1.9. The OSE SRPM makes OND DDS/ADS and OND SRPM/ORO RPM aware of the acceptable REMS Assessment Methodology submission.
1.10. The OSE SRPM schedules meetings with the SMEs and/or OND DDS/ADS, if necessary.

2. Initiating Review of REMS Assessment Methodology

[16] For review of certain REMS Assessment Methodologies (e.g., drug use, epidemiology, or pharmacovigilance studies for a REMS assessment), the DMAMES RAA will collaborate with the SME during the triage step to assist in determining if the submission is missing information necessary for review.

2.1. The DMAMES RAA initiates the review of the proposed REMS Assessment Methodology submission. To complete the review, the DMAMES RAA may perform one or more of the following activities:
   2.1.1. Meets with ATL and/or SMEs to discuss the timeline for completing the review and to discuss the proposed REMS Assessment Methodology if issues are identified.
   2.1.2. Drafts an IR if clarifying information is necessary to complete the review. Sends the IR to the ATL for clearance.

2.2. The SME(s) initiate(s) review of assigned portions of the REMS Assessment Methodology submission, which includes one or more of the following activities:
   2.2.1. Meet(s) with DMAMES RAA and ATL to discuss the timeline for completing the review and to discuss the proposed REMS Assessment Methodology if issues are identified.
   2.2.2. Draft(s) an IR if clarifying information is necessary to complete the review. Share(s) with the DMAMES RAA and ATL.

3. Issuing Information Requests

3.1. The DMAMES Director or designee will clear the IR.

3.2. The DMAMES ATL or RAA will send the final cleared IR language to the OSE SRPM through the CDER EIS.

3.3. The OSE SRPM issues the IR to the applicant(s)[17] .

4. Receipt of Responses to Information Requests

4.1. The OSE CPMS notifies the OSE SRPM of the response to an IR received in the ERKS.

4.2. The OSE SRPM notifies the DMAMES ATL, RAA, and SMEs within 3 calendar days of receipt that the IR response has been received.

4.3. The DMAMES ATL, RAA, and SMEs review the IR response to determine if the response is acceptable.
   4.3.1. If the response contains additional information that requires additional time to review:[18]
      4.3.1.1. The DMAMES RAA and ATL draft language for the *REMS Assessment Methodology Withdrawal Letter* and sends it to the OSE SRPM.
      4.3.1.2. The OSE SRPM drafts, obtains clearance, and uploads the *REMS Assessment Methodology Withdrawal Letter* to the CDER EIS.
      4.3.1.3. The DMAMES Director or designee clears and signs the *REMS Assessment Methodology Withdrawal Letter*.

5. Completion of REMS Methodology Review

[17] The OSE SRPM will issue IRs to the industry working group POC for any shared system REMS.

[18] A response requires additional time to review if it includes additional information outside the scope of the initial IR (e.g., the applicant submits additional questions, makes unsolicited revisions to the methodology, provides lengthy or complex response to an FDA question, or amends original submission materials with new information).

5.1. The SMEs draft their assigned section if the review is integrated or a separate review, obtain clearance through their management, and share the review with the DMAMES RAA by the agreed upon due date.
5.2. If SMEs draft a separate review, SMEs draft a summary of their review for the DMAMES RAA to incorporate into the DMAMES REMS Assessment Methodology Review.
5.3. DMAMES RAA sends the review to the SMEs to ensure their summary has been incorporated appropriately.
5.4. The SMEs, as applicable, DMAMES ATL, DMAMES Director or designee, clear the final DMAMES REMS Assessment Methodology Review.
5.5. The DMAMES RAA will send the recommendations/comments that will be included in the *REMS Assessment Methodology General Advice Letter* to the OND DDS/ADS and OND SRPM/RPM, or OGD OSCE REMS Coordinator.
5.5.1. The OND DDS/ADS, OND SRPM/RPM, or OGD OSCE REMS Coordinator will provide a response by the requested date.
5.6. The DMAMES RAA uploads the final DMAMES REMS Assessment Methodology Review into the CDER EIS for signatures by the DMAMES ATL, DMAMES director or designee, and SMEs who contributed to the REMS Assessment Methodology Review.
5.6.1. The DMAMES RAA ensures that the OSE SRPM is notified of entry through the CDER EIS.

6. Communication of Comments to Applicant(s)

6.1. The OSE SRPM drafts the *REMS Assessment Methodology General Advice Letter* using the letter ready comments from the final REMS Assessment Methodology Review.
6.2. The OSE SRPM obtains clearance and uploads the *REMS Assessment Methodology General Advice Letter* to the CDER EIS.
6.3. The DMAMES Director or designee clears and signs the *REMS Assessment Methodology General Advice Letter* to be issued.

7. Receipt of Withdrawal Request During the Review

7.1. The OSE CPMS notifies the OSE SRPM of the request to withdraw the REMS Assessment Methodology submission.
7.2. The OSE SRPM drafts, obtains clearance, and signs the *REMS Assessment Methodology – Acknowledge Withdrawal L*etter in the CDER EIS.

REFERENCES[19]

1. Draft Guidance for Industry: REMS Assessment: Planning and Reporting (February 2019). Available at: https://www.fda.gov/regulatory-

[19] When final, draft guidances will represent the FDA's current thinking on this topic. 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.

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 (February 2019). Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/survey-methodologies-assess-rems-goals-relate-knowledge.
3. MAPP 4151.8, Rev. 1 Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER Available at: https://www.fda.gov/media/157807/download.

DEFINITIONS

CDER Electronic Information System (EIS) – a "system that contains and provides access to computerized Federal records and other information".[20] Examples include Microsoft SharePoint Online and CDER Nexus.

CDER Electronic Records Keeping Systems (ERKS) – the authoritative data source for a given data element or piece of information within an information management system. This definition is specific to CDER's information technology strategy and infrastructure. Examples include Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), CDER Informatics Platform – Panorama, Documentum – Records Management Client (RM Client), and Electronic Document Room (EDR).[21]

REMS Assessment Methodology – a submission containing proposed methodological approaches and study protocols used to assess a REMS program.

REMS Assessment Methodology Letters:

REMS Assessment Methodology Acknowledgement Letter –communicates to the applicant(s) the PDUFA goal date to complete the review and issue recommendations.

REMS Assessment Methodology Acknowledge Withdrawal Letter – acknowledges the applicant(s) request to withdraw their submission.

REMS Assessment Methodology General Advice Letter –communicates to the applicant(s) the recommendations from the review of the REMS Assessment Methodology

REMS Assessment Methodology Incomplete Letter –communicates to the applicant(s) that the REMS Assessment Methodology is missing significant information necessary for review.

REMS Assessment Methodology Withdrawal Letter –communicates to the applicant(s) that their submission is withdrawn and provides the reason.

REMS Assessment Report – refers to the document submitted by applicants that includes the findings or results generated from the evaluation of the REMS program as specified in the REMS Assessment Plan.

[20] See 36 CFR 1236.2.
[21] See MAPP 7600.11, *CDER Electronic Record Keeping Systems* (available at: https://www.fda.gov/media/89742/download)

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
3/25/2024	Initial	New MAPP