POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

Review of Risk Evaluation and Mitigation Strategy (REMS) Assessment Reports`

Table of Contents

PURPOSE

- This MAPP describes how the Center for Drug Evaluation and Research (CDER) will review the risk evaluation and mitigation strategy (REMS) Assessment Reports that are submitted to the FDA as required under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1).

- This MAPP also describes how CDER will notify applicants when REMS Assessment Reports are not submitted on time, are submitted with missing required information, or the submitted information requires additional review time to make a determination as to whether the REMS is meeting its goal(s).

BACKGROUND

Section 505-1 of the 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]

A REMS may include a Medication Guide, patient package insert, 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.[3]

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, 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.

FDA generally does not require submission of REMS Assessment Reports for abbreviated new drug applications (ANDAs) that are part of a shared system REMS with an NDA; however, ANDA applicants should contribute to the assessment findings for shared system REMS. For shared system REMS or separate REMS comprised only of ANDA(s), often referred to as ANDA-only REMS, FDA requires submission of REMS Assessment Reports from the ANDA holders.

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

[1] Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., NDAs) or (j) (i.e., ANDAs) of the FD&C Act and to applications submitted or licensed under section 351 (i.e., BLAs) of the Public Health Service Act (PHS Act) (42 U.S.C. 262).
[2] See 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 sections 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.

Agency's thinking for this purpose.[7]

POLICY

- CDER conducts its review of REMS Assessment Reports in accordance with CDER's policies on equal voice and, if necessary, dispute resolution.[8]

- CDER retains records related to the review of REMS Assessment Reports within the CDER Electronic Record Keeping Systems (ERKS) as applicable.[9]
- CDER completes its review of the REMS Assessment Report and issues the *REMS Assessment Acknowledgment Letter* within 180 calendar days from receipt of the REMS Assessment Report, unless circumstances exist to extend the timeline for the review.[10]
    - For an individual applicant REMS: The receipt of the REMS Assessment Report to the individual NDA/BLA/ANDA will determine the start of the timeline and the issuance of the *REMS Assessment Acknowledgment Letter* will mark completion of the review for purposes of determining duration of the review activity.
    - For a shared system REMS that does not use a Drug Master File (DMF) or for a REMS with multiple applicants: The receipt of the REMS Assessment Report to the individual NDA/BLA (or ANDA, if applicable) will determine the start of the timeline and the issuance of the *REMS Assessment Acknowledgment Letter* will mark completion of the review for purposes of determining duration of the review activity.
    - For a shared system REMS that uses a DMF: The receipt of the REMS Assessment Report to the DMF will determine the start of the timeline and archiving the nonapplicant-specific copy of the *REMS Assessment Acknowledgment Letter* in the DMF will mark completion of the review for purposes of determining duration of

[7] For the guidance related to REMS assessments, see the References section.
[8] For more information on equal voice, see MAPP 4151.8, *Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER*. Available at: https://www.fda.gov/media/157807/download.
[9] 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).
[10] Circumstances that may result in extending the timeline for the review beyond 180 calendar days include additional data received in response to an IR, policy or methodological issues identified during the review, or data submissions requiring complex analyses.

the review activity.

- CDER issues a *Grant or Deny REMS Assessment Extension Request Letter* to respond to an applicant's proactive request for an extension in which to submit one or more parts of the REMS Assessment Report or the entire REMS Assessment Report.

- CDER issues a *Notification of Missing REMS Assessment Report Letter* if the REMS Assessment Report is not received by the due date.[11]

- CDER issues a *Missing REMS Assessment Information – Additional Information Required Letter* if the REMS Assessment Report is missing required information.[12]

- CDER issues a *Review Extension - REMS Assessment Report Letter* if the timeline for review of a REMS Assessment Report will be extended when data provided in response to an information request (IR) or other circumstances exist that require more time to review the submission (and could result in more than 180 calendar days for completing the review).[13]

RESPONSIBILITIES

- The following CDER offices contribute to the REMS Assessment Report Review activities described in this MAPP:
    - Office of Surveillance and Epidemiology (OSE)
    - Office of New Drugs (OND)[14]
    - Office of Compliance (OC)
    - Office of Generic Drugs (OGD)/Office of Safety and Clinical Evaluation (OSCE)
    - Other offices, as needed, including the following:

[11] For all REMS that include both NDAs and ANDAs, the REMS Assessment Report is due by the date specified in the approved REMS timetable. For all ANDA applicants and ANDA-only REMS, the REMS Assessment Report is due by the date all ANDAs are required to submit assessments at pre-specified intervals that are appended to the approval letter.
[12] For the purpose of this MAPP, "missing required information" refers to any information (e.g., drug utilization, surveillance data, knowledge survey findings) that is required in the current REMS Assessment Plan in the relevant approval letter or other REMS Assessment Letter but was not included in the submitted REMS Assessment Report.
[13] See footnote 10.
[14] In addition to other OND offices, the OND Division of Pediatric and Maternal Health (DPMH) is involved for all REMS that address teratogenicity or embryofetal toxicity.

- Office of Translational Science (OTS)/Office of Biostatistics (OB)
- Office of Medical Policy (OMP)[15]
- Office of Pharmaceutical Quality (OPQ)
- Office of Regulatory Policy (ORP).

Core REMS Assessment Review Team

- Consists of representatives from OSE, including the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES), Division of Risk Management (DRM), Division of Pharmacovigilance (DPV), Division of Epidemiology (DEPI), Office of Medication Error Prevention and Risk Mitigation (OMEPRM), Office of Pharmacovigilance and Epidemiology (OPE), and Project Management Staff (PMS).[16]
- Reviews all or portions of the REMS Assessment Report, conducts analyses of other data, and considers new or emerging safety data to inform the REMS assessment review.
- Prepares the draft REMS Assessment Report Review that includes findings from the review of the REMS Assessment Report and other relevant information, conclusions on whether the REMS is meeting its goal(s), and recommendations for next steps.
- Incorporates input from the CDER REMS Assessment Team into the draft REMS Assessment Report Review and finalizes the Review or separate subject matter expert (SME) review(s), if applicable, within the specified timeframe.
- Reviews meeting materials and participates in meetings, including the Core REMS Assessment Review Team meetings and CDER REMS Assessment Team meetings.

CDER REMS Assessment Team

- Consists of representatives from OND, OSE, OC, OGD, and other CDER offices as needed to provide input for REMS assessments.
- Informs the Core REMS Assessment Team of safety issues or other regulatory actions that may impact the REMS assessment.
- Reviews the draft REMS Assessment Report Review to provide comments on the Core REMS Assessment Review Team's findings

[15] The OMP Patient Labeling Team is involved for all REMS that include a Medication Guide and the Office of Prescription Drug Promotion (OPDP) is involved for any promotional concerns.
[16] Representatives from other CDER offices may be included as needed for the review of the REMS Assessment Report.

before the Core REMS Assessment Review Team finalizes the review.

- Discusses and strives for alignment with the Core REMS Assessment Team's conclusions on whether the REMS is meeting its goal(s) and recommendations for next steps.
- Participates in meetings, including the CDER REMS Assessment Team and REMS Oversight Committee (ROC) meetings as applicable.

OC REMS Compliance Team

- Consists of representatives from the Office of Scientific Investigations (OSI) within OC.
- Oversees the management and coordination of OC activities regarding the submission and review of the REMS Assessment Report.
- Tracks receipt of REMS Assessment Reports from applicants and notifies the OSE SRPM, OND SRPM, and OGD REMS Coordinator of REMS Assessment Report submissions that are due within 30 calendar days or are overdue.
- Attends the Core REMS Assessment Team and/or CDER REMS Assessment Team meetings and provides input as needed on the conclusions, recommendations, and other issues related to the REMS.

OGD/OSCE Division of Clinical Safety and Surveillance (DCSS) Director or Designee

- Serves as the signatory for REMS Assessment Letters issued to ANDA applicants for ANDA-only REMS.

OGD REMS Coordinator

- Oversees the management and coordination of OGD activities regarding the review of the REMS Assessment Report for ANDA-only REMS.
- Coordinates communication between OGD and OSE.
- Ensures that REMS Assessment Report submissions to the ANDAs are accurately coded in the CDER ERKS, and submits change requests, as appropriate.
- Notifies the assigned OSE SRPM of REMS assessment-related submissions when received under the ANDA-only REMS.
- Drafts, coordinates review and clearance, and issues the appropriate REMS Assessment Letter to ANDA applicants for ANDA-only REMS.
- For an ANDA-only REMS, issues applicant-specific REMS assessment-related IRs to ANDA applicants.

- For ANDA-only shared system REMS that use a DMF, prepares a nonapplicant-specific copy of the REMS Assessment Letter and provides it to the OSE SRPM if applicable.
- Attends the CDER REMS Assessment Team meetings and provides input as needed on the conclusions, recommendations, and other issues related to the REMS.

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

- Serves as the signatory for REMS Assessment Letters issued to NDA/BLA applicants for REMS, including shared system REMS.
- Oversees the OND review division activities regarding REMS assessments and serves as the liaison between the OND clinical division(s) and the CDER REMS Assessment Team.
- Provides input and seeks alignment with the DMAMES director on the Core REMS Assessment Review Team's conclusions, recommendations, and other issues related to assessing whether the REMS is meeting its goal(s).
- Updates the CDER REMS Assessment Team on safety issues or other regulatory actions that may impact the REMS assessment.
- Participates in meetings, including the CDER REMS Assessment Team and ROC meetings, as applicable.

OND Regulatory Project Manager (RPM)

- Serves as point of contact (POC), as applicable, for communications with the NDA/BLA applicant.
- Notifies the OND SRPM and OSE SRPM, as applicable, when a REMS assessment-related submission is received.[17]

OND Safety Regulatory Project Manager (SRPM)[18]

- Serves as the POC for all communications with NDA/BLA applicants for individual applicant REMS.
- Coordinates communication between OND and OSE.

[17] If there is no OND SRPM or OSE SRPM assignment in the submission in the CDER ERKS, the OND RPM will notify the OND SRPM and OSE SRPM that a submission has been received. Base assignments should be requested in the CDER ERKS by the OND SRPM and/or OSE SRPM so that future submissions will be received by relevant staff.

[18] The OND SRPM generally fills this role; however, for some OND divisions that do not have an SRPM this role will be filled by the OND RPM. There may be circumstances based on workload where the OND SRPM and OND RPM may make arrangements for the OND RPM to fill this role.

- Drafts, coordinates review and clearance, and issues the appropriate REMS Assessment Letter to respective NDA/BLA applicants.
- Serves as a member of the CDER REMS Assessment Team and attends meetings.
- Receives REMS assessment-related submissions and notifies the assigned OSE SRPM of REMS assessment-related submissions, as applicable.[19]
- Ensures that REMS Assessment Report submissions to NDAs/BLAs are accurately coded in the CDER ERKS, and submits change requests, as appropriate.
- For a shared system REMS that uses a DMF, prepares a nonapplicant-specific copy of the REMS Assessment Letter and provides it to the OSE SRPM.
- Issues IRs to NDA/BLA applicants.

OSE DMAMES Director or Designee

- Reviews and clears the final REMS Assessment Report Review.
- Provides input and seeks alignment with the DDS/ADS on the Core REMS Assessment Review Team's conclusions, recommendations, and other issues related to assessing whether the REMS is meeting its goal(s).
- Participates in meetings, including the CDER REMS Assessment Team and ROC meetings, as applicable.

OSE DMAMES REMS Assessment Analyst (RAA)

- Leads the Core REMS Assessment Team in the review of the REMS Assessment Report.
- Serves as the REMS assessment SME on the Core REMS Assessment Review Team and the CDER REMS Assessment Team.
- Determines if the submitted REMS Assessment Report is missing required information.
- In collaboration with the OSE SRPM, facilitates the Core REMS Assessment Review Team meetings and the CDER REMS Assessment Team meetings.
- Initiates and consolidates IRs to be sent to the applicant(s).
- Drafts, finalizes, and archives the REMS Assessment Report Review incorporating the input of the CDER REMS Assessment Team.

OSE DMAMES REMS Assessment Team Leader (ATL)

[19] If there is no OSE SRPM assignment in the submission in the CDER ERKS, the OND SRPM will notify the OSE SRPM that a submission has been received. Base assignments should be requested in the CDER ERKS by the OSE SRPM so that future submissions will be received by relevant staff.

- Works with the RAA to ensure timely review of the REMS Assessment Report.
- Informs the CDER REMS Assessment Team about progress on reviewing the REMS Assessment Report and whether there are issues that may impact the review timeline.
- Identifies, in collaboration with the RAA, SMEs who should be consulted for the review.
- Attends the Core REMS Assessment Review Team and the CDER REMS Assessment Review Team meetings and provides input on the conclusions, recommendations, and other issues related to the REMS.

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

- Serves as the REMS SME for the REMS design, requirements, and other regulatory activities that may impact the REMS.
- Attends the Core REMS Assessment Review Team and the CDER REMS Assessment Review Team meetings and provides input on the conclusions, recommendations, and other issues related to the REMS.

OSE Chief of Project Management Staff (CPMS)

- Triages and assigns an OSE SRPM when a REMS Assessment Report is submitted to the FDA.

OSE Safety Regulatory Project Manager (SRPM)

- Serves as the POC for communication with the Industry Working Group (IWG) POC for REMS Assessment Reports of shared system REMS, and the POC for the ANDA applicant for a separate REMS.
- Ensures that REMS Assessment Report submissions to the DMF and other REMS assessment submissions are accurately coded in the CDER ERKS, and submits change requests, as appropriate.
- Assigns the ATL to the REMS Assessment Report.
- Creates a designated collaborative shared workspace to house all work materials related to the review of the REMS Assessment Report.
- Issues collaboration requests for consults to SMEs as needed.
- In collaboration with the RAA, schedules and facilitates the Core REMS Assessment Review Team meetings and the CDER REMS Assessment Team meetings.
- Issues IRs to the IWG POC for a shared system REMS and/or the POC for the ANDA applicant for a separate REMS and archives the sent IR in

the CDER ERKS.

- Submits the completed ROC meeting request form to the ROC POC to discuss the REMS Assessment Report Review findings, as needed.
- For a shared system REMS that uses a DMF, provides the nonapplicant-specific copy of the REMS Assessment Letter to the IWG POC (after the letter has been finalized in the CDER ERKS for the individual NDAs/BLAs) and uploads a copy of the nonapplicant-specific REMS Assessment Letter to the CDER ERKS.

PROCEDURES

See Attachment 1 for a summary of REMS assessment communication responsibilities.

1. Monitoring for REMS Assessment Report Submissions

1.1. The OC REMS Compliance Team sends a report of upcoming REMS Assessment Reports to the OGD REMS Coordinator, OND SRPM, and the appropriate staff in DMAMES, DRM, and PMS.

1.2. The OC REMS Compliance Team monitors the CDER ERKS to confirm receipt of the REMS Assessment Report.

1.2.1. In response to an applicant's proactive request for an extension to submit a REMs Assessment Report or information in a Report:

1.2.1.1. The RAA and ATL draft language for the *Grant or Deny REMS Assessment Extension Request Letter* and send it to the OSE SPRM within 10 calendar days of receipt of the request.

1.2.1.2. The OSE SRPM sends an email with the draft language to the OND SRPM or to the OGD REMS Coordinator (if applicable)

1.2.1.3. The OND SRPM or OGD REMS Coordinator (if applicable):

1.2.1.3.1. Drafts the *Grant or Deny REMS Assessment Extension Request Letter*.

1.2.1.3.2. Coordinates review by the DMAMES ATL.

1.2.1.3.3. Coordinates clearance by the DDS/ADS or OGD/DCSS director or designee (if applicable).

1.2.1.3.4. Issues the *Grant or Deny REMS Assessment Extension Request Letter* to the applicant.

1.2.1.3.5. Ensures that the OC REMS Compliance Team and OSE SRPM are aware the letter was issued.

1.3. The OC REMS Compliance Team notifies the appropriate OSE SRPM, OND SRPM, or the OGD REMS Coordinator if the report has not been received by the due date.

1.3.1. If the REMS Assessment Report is not received within 30 calendar days of the due date, the OND SRPM or OGD REMS Coordinator (if applicable) sends the *Notification of Missing REMS Assessment Report Letter* to the applicant and ensures the OC REMS Compliance Team (CDER-OSI-REMS@fda.hhs.gov) and the OSE SRPM are aware the letter was issued.

1.3.1.1. The OC REMS Compliance Team monitors whether the REMS Assessment Report has been received by the date specified in the *Notification of Missing REMS Assessment Report Letter*.

1.3.1.2. If the REMS Assessment Report is not received by the date specified in the *Notification of Missing REMS Assessment Report Letter*, the OC REMS Compliance Team will discuss with DMAMES, OND, and/or OGD (for ANDA-only REMS) to determine next steps.

1.3.2. Once the REMS Assessment Report is received, review of the REMS Assessment Report will begin as described below.

2. Receipt and Triage of REMS Assessment Report

2.1. Within 5 calendar days of receipt of a REMS Assessment Report, the following tasks are completed in the CDER Electronic Information System:

2.1.1. The OSE CPMS and OND SRPM/OND RPM or OGD REMS Coordinator (if applicable) receive notification of the report receipt from the CDER Electronic Information System or CDER ERKS.

2.1.2. The OSE CPMS assigns the OSE SRPM.

2.1.3. The OSE SRPM assigns the ATL.

2.1.4. The ATL assigns the RAA.

2.2. Within 14 calendar days of receipt of a REMS Assessment Report, the following tasks are completed:

2.2.1. The ATL identifies the team member roles needed for the Core REMS Assessment Review Team and the CDER REMS Assessment Team.

2.2.2. The OSE SRPM assigns the appropriate person for each identified team member role.

2.2.3. The OSE SRPM creates an electronic folder on the designated collaborative shared workspace in the CDER Electronic Information System to house all work materials for members of the Core REMS Assessment Review Team and CDER Assessment Review Team.

3. Review of REMS Assessment Report for Missing Information

3.1. Within 15 calendar days of receipt of a REMS Assessment Report, the RAA reviews the REMS Assessment Report to determine if the REMS Assessment Report is missing any required information.

3.2. If the REMS Assessment Report is missing required information:

3.2.1. Within 20 calendar days of receipt of the REMS Assessment Report:

3.2.1.1. The ATL and RAA draft language for the *Missing REMS Assessment Information – Additional Information Required Letter* and send it to the OSE SRPM.

3.2.1.2. The OSE SRPM sends an email with the draft language to the OND SRPM or the OGD REMS Coordinator (if applicable) and copies the OC REMS Compliance Team on the email.

3.2.2. The OND SRPM or OGD REMS Coordinator (if applicable):

3.2.2.1. Drafts the *Missing REMS Assessment Information – Additional Information Required Letter*.

3.2.2.2. Coordinates review by the DMAMES ATL.

3.2.2.3. Coordinates clearance by the DDS/ADS or OGD/DCSS director or designee (if applicable).

3.2.2.4. Issues the *Missing REMS Assessment Information – Additional Information Required Letter* to the applicant within 30 calendar days of receipt of the REMS Assessment Report.

3.2.2.5. Ensures that the OC REMS Compliance Team and OSE SRPM are aware the letter was issued.[20]

3.2.3. If the missing information is not received by the date specified in the *Missing REMS Assessment Information – Additional Information Required Letter*, DMAMES, OND, and/or OGD (for ANDA-only REMS) will discuss with the OC REMS Compliance Team to determine next steps.

3.3. If the REMS Assessment Report is not missing any information, the ATL or RAA and OSE SRPM will complete the following tasks in the CDER Electronic Information System:

3.3.1. The ATL or RAA initiates collaboration requests to consult SMEs if needed.

3.3.1.1. The collaboration requests include a description of the information to be reviewed and desired completion date.

3.3.2. The OSE SRPM issues any collaboration requests to the SME.

4. Initiating Review of the REMS Assessment Report

4.1. The OSE SRPM schedules the Core REMS Assessment Review Team initial planning meeting to occur within 30 to 45 calendar days of receipt of the REMS Assessment Report.

4.2. The Core REMS Assessment Review Team performs a preliminary review of the REMS Assessment Report before the initial planning meeting.

[20] Base assignments should be requested in the CDER ERKS by the OC REMS Compliance Team and OSE SRPM so that notifications will be received by the appropriate staff.

4.3. At the initial planning meeting, the Core REMS Assessment Review Team:

4.3.1. Determines if the REMS Assessment Report requires more time to review (and could result in more than 180 calendar days for completing the review).

4.3.1.1. If determined that the REMS Assessment Report requires more time to review, the RAA and ATL draft language for the *Review Extension – REMS Assessment Report Letter* and send it to the OSE SRPM within 10 calendar days of the initial planning meeting.

4.3.1.2. The OSE SRPM sends an email with the draft language to the OND SRPM or to the OGD REMS Coordinator (if applicable).

4.3.1.3. The OND SRPM or OGD REMS Coordinator (if applicable):

4.3.1.3.1. Drafts the *Review Extension – REMS Assessment Report Letter*.

4.3.1.3.2. Coordinates review by the DMAMES ATL.

4.3.1.3.3. Coordinates clearance by the DDS/ADS or OGD/DCSS director or designee (if *applicable*).

4.3.1.3.4. Issues the *Review Extension – REMS Assessment Report Letter* to the applicant within 20 calendar days of receipt of the draft language from the OSE SRPM.

4.3.1.3.5. Ensures that the OSE SRPM is aware the letter was issued.

4.3.1.4. For a shared system REMS that uses a DMF, the OND SRPM or OGD REMS Coordinator (as applicable) prepares a nonapplicant-specific copy of the *Review Extension – REMS Assessment Report Letter* and provides it to the OSE SRPM.

4.3.1.5. For a shared system REMS, that uses a DMF, the OSE SRPM provides the nonapplicant-specific copy of the *Review Extension – REMS Assessment Report Letter* to the IWG POC and uploads the copy to the CDER ERKS.

4.3.2. Develops a workplan for conducting the review that includes, but is not limited to, determining:

4.3.2.1. Whether additional SME(s) are needed for review of the REMS Assessment Report.

4.3.2.2. If the written review will be an integrated review or if each SME will write a separate review, if applicable.

4.3.2.3. The frequency and purpose of meetings needed for the Core REMS Assessment Review Team.

4.3.2.4. The timelines for completing draft and final reviews, taking into consideration if any other regulatory actions or REMS review activities (e.g., pending REMS modifications) will impact review timelines.

4.3.2.5. The timeline for a meeting of the CDER REMS Assessment Team (scheduled to occur within 150 calendar days of receipt of the REMS Assessment Report).

4.3.2.6. Whether additional interim meetings are needed with the DDS/ADS or other members of the CDER REMS Assessment Team to discuss preliminary findings.

4.4. The OSE SRPM will share the workplan with the CDER REMS Assessment Team (including the OND SRPM/OND RPM and OGD REMS Coordinator) and will schedule meetings for the Core REMS Assessment Review Team and the meeting of the CDER REMS Assessment Team based on availability of required numbers.

5. Issuing Information Requests (IRs)

5.1. The ATL or RAA will begin to develop the IR:

5.1.1. Each SME on the Core REMS Assessment Review Team will prepare letter-ready comments for inclusion in an IR, if needed, for data or other information within the report that may require clarification, and then send their letter-ready comments to the RAA for inclusion in an IR.[21]

5.1.2. The RAA will consolidate the letter-ready comments received from each SME and send the consolidated letter-ready comments for the IR to the ATL for clearance.

5.1.3. If the ATL identifies a need to discuss the IR, the ATL will ask the OSE SRPM to schedule a meeting or add to the agenda for a regularly scheduled Core REMS Assessment Review Team meeting.

5.1.4. After the consolidated IR language is finalized and cleared by the ATL, the ATL or RAA will send the cleared IR language to the OSE SRPM.

5.2. For individual applicant REMS for NDAs/BLAs, the OSE SRPM sends the ATL- reviewed IR to the OND SRPM.

5.2.1. The OND SRPM initiates and coordinates review and clearance of the IR by the DDS/ADS and OND clinical division(s) and issues the IR to the applicant.

5.2.2. The OND SRPM archives the IR sent to the NDA/BLA applicants in the CDER ERKS.

5.3. For shared system REMS and ANDA-only REMS, the OSE SRPM sends the ATL-cleared IR to the IWG POC and/or the POC for the ANDA applicant, respectively.

[21] General methodology comments or comments on the format and content of the information in the REMS Assessment Report that affect future Assessment Reports, can be provided to the applicant in a General Advice Letter prior to the completion of the REMS Assessment Report Review. Questions and comments that are specific to a submitted REMS Assessment Report under review should be communicated as an IR.

5.3.1. The OSE SRPM archives the IR sent to the IWG POC (for shared system REMS), and/or the POC for the ANDA applicant (for an ANDA-only REMS) in the CDER ERKS.

6. Receipt of Responses to Information Requests (IRs)

6.1. The OSE SRPM and OND SRPM/OND RPM or OGD REMS Coordinator (if applicable) receive notification that the IR response from an applicant has been received from the CDER Electronic Information System or CDER ERKS.

6.2. The OSE SRPM notifies the Core REMS Assessment Review Team within 3 calendar days of being notified that the response to an IR has been received.

6.3. The Core REMS Assessment Review Team reviews the response to the IR to determine if the response includes additional data that requires more time to review (and could result in more than 180 calendar days for completing the review).

6.4. If the additional data require more time to review:

6.4.1. Within 20 calendar days of receipt of the response to the IR:

6.4.1.1. The RAA and ATL draft language for the *Review Extension – REMS Assessment Report Letter* and send it to the OSE SRPM.

6.4.1.2. The OSE SRPM sends an email with the draft language to the OND SRPM or the OGD REMS Coordinator (as applicable).

6.4.2. The OND SRPM or OGD REMS Coordinator (if applicable):

6.4.2.1. Drafts the *Review Extension – REMS Assessment Report Letter*.

6.4.2.2. Coordinates review by the DMAMES ATL.

6.4.2.3. Coordinates clearance by the DDS/ADS or OGD/DCSS director or designee (if applicable).

6.4.2.4. Issues the *Review Extension – REMS Assessment Report Letter* to the applicant within 30 calendar days of receipt of the response to the IR.

6.4.2.5. Ensures that the OSE SRPM is aware the letter was issued.

6.4.2.6. For a shared system REMS that uses a DMF, the OND SRPM or OGD REMS Coordinator (as applicable) prepares a nonapplicant-specific copy of the *Review Extension – REMS Assessment Report Letter* and provides it to the OSE SRPM.

6.4.2.7. For a shared system REMS that uses a DMF, the OSE SRPM provides the nonapplicant-specific copy of the *Review Extension – REMS Assessment Report Letter* to the IWG POC and uploads the copy to the CDER ERKS.

7. Preparing the Draft REMS Assessment Report Review

7.1. The RAA posts the review template for the REMS Assessment Report Review on the designated collaborative shared workspace.

7.2. The Core REMS Assessment Review Team drafts the REMS Assessment Report Review that includes key findings from the review of the report, preliminary conclusions, recommendations for next steps (including steps to address relevant issues such as concerns with the methodological approaches for the assessment or new safety or compliance findings).

7.2.1. For integrated reviews, the RAA and other SME(s) draft their assigned section(s) of the draft REMS Assessment Report Review.

7.2.2. If the SME(s) provides a separate review, the RAA will share the draft REMS Assessment Report Review with the SME(s) for review and comment.

7.2.2.1. The SME(s) will share their draft separate review with the Core REMS Assessment Review Team and provide a written summary to be included in the draft REMS Assessment Report Review, if applicable.

7.3. The ATL for the RAA and team leads and/or directors for the other SMEs who contributed to the REMS Assessment Report Review clear the draft REMS Assessment Report Review.

7.4. The DMAMES director or designee preliminarily clears the draft REMS Assessment Report Review.

8. CDER REMS Assessment Team Meeting and Review

8.1. The OSE SRPM will schedule a meeting of the CDER REMS Assessment Team to occur no later than 150 calendar days post receipt of the REMS Assessment Report.

8.1.1. If a *Review Extension – REMS Assessment Report Letter* has been issued to the applicant, the OSE SPRM will notify the CDER REMS Assessment Team to discuss rescheduling the meeting.

8.2. At least 14 calendar days before the scheduled CDER REMS Assessment Team meeting:

8.2.1. The RAA provides the OSE SRPM the link to the draft REMS Assessment Report Review.

8.2.2. The OSE SRPM provides the CDER REMS Assessment Team a link to the draft REMS Assessment Report Review with a request that the CDER REMS Assessment Team members review and comment on the Core REMS Assessment Review Team's conclusions, recommendations, and other issues related to assessing whether the REMS is meeting its goal(s).

8.2.2.1. The CDER REMS Assessment Team members should provide their comments in the draft REMS Assessment Report Review and to the

RAA at least 3 calendar days prior to the scheduled CDER REMS Assessment Team meeting, and be prepared to discuss the conclusions, recommendations, and other issues related to assessing whether the REMS is meeting its goal(s).

8.3. The RAA will review comments provided by the CDER REMS Assessment Team on the draft REMS Assessment Report Review to inform whether the scheduled CDER REMS Assessment Team meeting should be cancelled or held as scheduled.

8.3.1. If the draft REMS Assessment Report Review includes a preliminary conclusion that the REMS is meeting its goal(s) and does not include any issues of concern, and the CDER REMS Assessment Team concurs, then the RAA will confer with the ATL and request the OSE SRPM cancel the scheduled CDER REMS Assessment Team meeting.

8.3.1.1. The RAA will begin the process of finalizing the REMS Assessment Report Review that includes draft language for the OND SRPM or OGD REMS Coordinator (as applicable) to incorporate into the *REMS Assessment Acknowledgment Letter*.

8.3.2. If the draft REMS Assessment Report Review includes a preliminary conclusion that the REMS is not meeting (or is partially meeting) its goal(s), or it cannot be determined if the REMS is meeting its goals, or the CDER REMS Assessment Team does not concur or has other issues for discussion, then the scheduled CDER REMS Assessment Team meeting will be held and proceed as described below.

8.4. The CDER REMS Assessment Team members will attend the scheduled meeting to discuss and provide input on findings by the Core REMS Assessment Team, including:

8.4.1. Is the REMS meeting its goal(s)?

8.4.2. Does the REMS Assessment Plan require revisions?

8.4.3. Is further analysis needed to evaluate if the REMS may require modification based upon the findings from the review of the REMS Assessment Report?[22]

8.4.4. Is the REMS still necessary to ensure the benefits of the drug product outweigh the risks?

8.4.5. Are there are any other issues that impact the benefit-risk assessment of the drug product?

8.4.6. Are there are any additional steps (e.g., labeling revisions) needed to address findings or other relevant issues?

[22] For more information related to REMS modifications, see MAPP 4191.1, *Risk Evaluation and Mitigation Strategies Modifications and Revisions*. Available at: https://www.fda.gov/media/128782/download.

8.4.7. Do any assessment findings (e.g., REMS continually not meeting goals) require discussion or input from the ROC?

8.4.8. Should any REMS assessment findings be discussed at an FDA Drug Safety and Risk Management Advisory Committee or other advisory committee meeting?[23]

8.4.9. What are the plans to finalize the REMS Assessment Report Review and draft the *REMS Assessment Acknowledgment Letter*?

8.5. The OSE SRPM captures meeting attendance and summarizes meeting discussions, team conclusions, and action items. The OSE SRPM will distribute the meeting summary within 5 calendar days to all the attendees of the CDER REMS Assessment Team meeting.

9. Completion of the REMS Assessment Report Review

9.1. The RAA incorporates the discussion, recommendations, and conclusions of the CDER REMS Assessment Team into the REMS Assessment Report Review.

9.2. The updated draft REMS Assessment Report Review will be available on the designated collaborative shared workspace for final review by the CDER REMS Assessment Team.

9.2.1. The RAA incorporates any additional comments and initiates clearance.

9.3. The ATL for the RAA and team leads and/or directors for the other SMEs who provided sections of the REMS Assessment Report Review clear the REMS Assessment Report Review.

9.4. The DMAMES director or designee clears the final REMS Assessment Report Review.

9.5. At least 3 weeks prior to the ***internal goal date***, the RAA uploads the final REMS Assessment Report Review into the CDER ERKS for signatures by the ATL, DMAMES director or designee, and others who contributed to or cleared the REMS Assessment Report Review.

9.5.1. The RAA ensures that the Core REMS Assessment Review Team and CDER REMS Assessment Team (including the OND SRPM and OGD REMS Coordinator) receive a copy of the review in CDER ERKS.

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

10.1. The OND SRPM or OGD REMS Coordinator (if applicable), referencing language from the final REMS Assessment Report Review, drafts the *REMS Assessment Acknowledgment Letter*.

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

10.2. The OND SRPM or OGD REMS Coordinator uploads the draft *REMS Assessment Acknowledgment Letter* to the CDER Electronic Information System to be reviewed by DMAMES.

10.3. The RAA, ATL, and DMAMES Director or designee reviews the language for the *REMS Assessment Acknowledgment Letter*.

10.4. The OND SRPM or OGD REMS Coordinator (if applicable) uploads the *REMS Assessment Acknowledgment Letter* to the CDER Electronic Information System for review and to obtain clearance from the DDS/ADS or OGD/DCSS director or designee (if applicable).

10.5. The DDS/ADS clears and signs the *REMS Assessment Acknowledgment Letter* to be issued to the NDA/BLA applicant(s).

10.5.1. The OND SRPM issues the finalized *REMS Assessment Acknowledgment Letter* to the NDA/BLA applicant by the internal goal date.

10.6. The OGD/DCSS director or designee clears and signs the *REMS Assessment Acknowledgment Letter* for ANDA applicant(s) for ANDA-only REMS.

10.6.1. The OGD REMS Coordinator provides the finalized *REMS Assessment Acknowledgment Letter* to the ANDA applicant as applicable by the internal goal date.

10.7. For a shared system REMS with a DMF:

10.7.1. The OND SRPM or OGD REMS Coordinator (as applicable) prepares a nonapplicant-specific copy of the *REMS Assessment Acknowledgment Letter* and provides it to the OSE SRPM.

10.7.2. The OSE SRPM provides the nonapplicant-specific copy of the *REMS Assessment Acknowledgment Letter* to the IWG POC and uploads the copy to the CDER ERKS.

REFERENCES[24]

1. Draft Guidance for Industry: REMS Assessment: Planning and Reporting (February 2019).
2. Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge (February 2019).
3. Draft Guidance for Industry: Development of a Shared System REMS (June 2018).
4. Draft Guidance for Industry: Use of a Drug Master File for Shared System REMS Submissions (November 2017).
5. Guidance for Industry: Risk Evaluation and Mitigation Strategies: Modifications and Revisions (June 2020).

DEFINITIONS

- **Abbreviated New Drug Application (ANDA)-only REMS** – for the purpose of this MAPP, refers to a separate REMS that includes one or more ANDA drug products only (does not include NDAs or BLAs).
- **CDER Electronic Information System** – a "system that contains and provides access to computerized Federal records and other information".[25] Examples include Microsoft SharePoint Online and CDER Nexus.
- **CDER Electronic Record 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).[26]
- **CDER REMS Assessment Team** – CDER-wide team consisting of representatives from OND (DDS/ADS, OND SRPM/OND RPM, OND clinical divisions), OSE (including the Core REMS Assessment Review Team),

[24] When final, draft guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch.

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

OGD/OSCE (OGD REMS Coordinator), OC REMS Compliance Team, and other CDER staff as deemed necessary for providing input for REMS assessments.

- **Core REMS Assessment Review Team** – consists of representatives from OSE (including the DMAMES RAA and ATL, DRM RMA and TL, DPV reviewer and TL, DEPI reviewer and TL, OPE cross-discipline safety advisor, and PMS SRPM and CPMS) and others within CDER as necessary to review the REMS Assessment Report, conduct analyses of related data, and prepare and finalize the REMS Assessment Report Review.
- **Individual Applicant REMS** – For the purpose of this MAPP, refers to a REMS that encompasses only one NDA, BLA or ANDA applicant for one or more prescription drug products.
- **Industry Working Group (IWG)** – refers to the working group that the applicants have formed to develop and implement a shared system REMS.
- **Industry Working Group Point of Contact (IWG POC)** – The single representative for the IWG who facilitates communications between FDA and the IWG about the shared system REMS.
- **Internal Goal Date** – For the purpose of this MAPP, begins on the receipt date of the REMS Assessment Report and ends 180 calendar days later with issuance of the *REMS Assessment Acknowledgment Letter*, unless circumstances exist to extend the timeline for the review.
- **Nonapplicant-specific Copy** – refers to a de-identified (i.e., applicant information in the letter removed) copy of a REMS Assessment Letter for shared system REMS with a DMF.
- **REMS Assessment Letters:**
    - ***Grant or Deny REMS Assessment Extension Request Letter*** – communicates response to an applicant's proactive request for an extension in which to submit one or more parts of the REMS Assessment Report (e.g., results of survey findings) or the entire REMS Assessment Report.
    - ***Missing REMS Assessment Information – Additional Information Required Letter*** – communicates to the applicant that the REMS Assessment Report is missing required information and provides the date that the missing information must be provided.
    - ***Notification of Missing REMS Assessment Report Letter*** – communicates to the applicant that the REMS Assessment Report was not received according to the approved timetable for submission of REMS Assessments and provides the date that the REMS Assessment Report must be submitted.
    - ***REMS Assessment Acknowledgment Letter*** – communicates the findings, conclusions, and recommendations from the FDA review of the REMS Assessment Report to the REMS application holder.

  - ***Review Extension - REMS Assessment Report Letter*** – communicates that an extension of the FDA's review time for the REMS Assessment is warranted to allow FDA to complete their review.

- **REMS Assessment Plan** – refers to the specific plan for how the applicant intends to assess the performance of the REMS in meeting its risk mitigation goal(s). The REMS Assessment Plan metrics are in the REMS approval letter and described in detail in the REMS Supporting Document.
- **Risk Evaluation and Mitigation Strategy (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.
- **REMS Assessment Report Review** – documents the findings, conclusions, and recommendations from the CDER REMS Assessment Review Team on the review of a REMS Assessment Report.
- **REMS Oversight Committee (ROC)** – a committee comprised of CDER senior leadership that provides advice on staff recommendations to address REMS-related topics and/or application-specific REMS issues. The ROC ensures CDER maintains a consistent approach to decision-making related to elements to assure safe use (ETASU) REMS and the design, implementation, and assessment of REMS.
- **Separate REMS** – refers to any separate REMS system used by one or more applicants that uses an aspect of the required ETASU(s) that is comparable to the approved REMS for the reference listed drug and is expected to achieve the same level of safety.
- **Shared System REMS** – refers to a REMS that encompasses multiple prescription drug products and is developed and implemented jointly by two or more applicants.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
12/18/2019	Initial	NA
3/25/2024	Rev 1.	Changes due to office reorg. Updated procedures section
12/12/2024	Admin	Admin Changes

ATTACHMENT: SUMMARY OF REMS ASSESSMENT COMMUNICATION RESPONSIBILITIES

The following table summarizes the communication responsibilities of the OND SRPM or designee, OSE SRPM, and OGD REMS Coordinator for drafting and sending IRs and letters related to REMS assessments. The responsibilities depend on whether the communications are for an individual applicant REMS or a shared system REMS.

Type of Communication	**Individual NDA/BLA REMS**	**Shared System REMS that include NDAs/BLAs/ANDAs**	**ANDA-Only REMS (does not include NDAs/BLAs)**
IRs	OND SRPM or designee	OSE SRPM OND SRPM if the IR is for the individual NDA/BLA application (e.g., drug use for a specific product) OGD REMS Coordinator if the IR is for an individual ANDA application (e.g., drug use for a specific product)	OSE SRPM OGD REMS Coordinator if the IR is for the individual ANDA application (e.g., drug use for a specific product)
Letters related to REMS Assessments • *Grant or Deny REMS Assessment Extension Request Letter* • *Missing REMS Assessment Information – Additional Information Required Letter* • *Notification of Missing REMS Assessment Report Letter* • *REMS Assessment Acknowledgment Letter*	OND SRPM or designee	OND SRPM or designee (to the NDA/BLA applicant(s) in the shared system) OSE SRPM sends a nonapplicant-specific copy to the IWG POC and uploads a copy in the CDER ERKS	OGD REMS Coordinator (if there is a DMF, sends OSE SRPM a nonapplicant-specific copy addressed to IWG POC). Issues additional applicant-specific letters as needed. OSE SRPM sends a nonapplicant-specific copy to the IWG POC and uploads a copy in the CDER ERKS

Type of Communication	Individual NDA/BLA REMS	Shared System REMS that include NDAs/BLAs/ANDAs	ANDA-Only REMS (does not include NDAs/BLAs)
• *Review Extension – REMS Assessment Report Letter* • *General Advice Letter*			