POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

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

Table of Contents

PURPOSE

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

- Developing a **single, shared system (SSS) risk evaluation and mitigation strategy (REMS)**[1] with elements to assure safe use (ETASU) for a reference listed drug (RLD) and abbreviated new drug application(s) (ANDA(s)) that reference the RLD during the review of the ANDA(s), and

- Developing a **separate REMS** that uses a different, comparable aspect of the Reference Listed Drug (RLD) ETASU (if applicable) for an ANDA during the review of the ANDA.

[1] Terms that appear in bold type upon first use are defined on pages 19-20.

This MAPP covers the process for the development of a SSS REMS or separate REMS and the determination that a SSS REMS or separate REMS is acceptable for final or tentative approval of the ANDA. This MAPP does not provide information on other Agency actions (e.g., complete response letters) associated with a particular application. This MAPP also does not describe the policy, responsibilities and procedures for the development of a **shared system REMS** for multiple NDAs or ANDAs, submitted under section 505(b)(1), (b)(2), or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), or multiple biologics license applications (BLAs), submitted under section 351(a) or (k) of the Public Health Service Act.

BACKGROUND

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[2] created section 505-1 of the FD&C Act, which authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks.[3] A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may include 1 or more of the following components: a Medication Guide (or patient package insert) to provide risk information to patients,[4] a communication plan to disseminate risk information to health care providers,[5]and/or certain packaging or safe disposal system for drug products that pose a serious risk of abuse or overdose. FDA may also require certain ETASU when such elements are necessary to mitigate specific serious risks associated with a drug.[6] ETASU may include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions.

Certain REMS with ETASU may also include an implementation system through which the applicant is able to monitor and evaluate implementation of the ETASU and work to improve their implementation.[7] Finally, a REMS generally must have a timetable for submission of assessments of the strategy.[8]

An ANDA referencing a drug with a REMS with ETASU is subject to the same ETASU requirements as the RLD. The ANDA may use a SSS with the listed drug or a different,

[2] Public Law 110-85.
[3] Section 505-1(a) of the FD&C Act.
[4] Section 505-1(e)(2) of the FD&C Act.
[5] Section 505-1(e)(3) of the FD&C Act.
[6] Section 505-l(f)(3) of the FD&C Act.
[7] Section 505-1(f)(4) of the FD&C Act.
[8] Section 505-1(d) of the FD&C Act.

comparable aspect of the ETASU[9] (referred to in this MAPP as a "separate REMS").[10] FDA may require an ANDA to use a SSS with the listed drug if it determines that no separate REMS could satisfy the necessary requirements.[11]

The Generic Drug User Fee Amendments (GDUFA) was enacted in 2012 to speed access to safe and effective generic drugs to the public and reduce costs to industry.[12] Under GDUFA, FDA committed to review and act on complete electronic ANDAs within 10 months after the date of submission.[13] On August 18, 2017, GDUFA was reauthorized through September 2022 (GDUFA II). Under GDUFA II, FDA committed to continue to review and act on 90% of standard original ANDAs within 10 months of the date of submission, and to also review and act on certain priority original ANDAs within eight months of the date of ANDA submission.[14]

POLICY

- When a new ANDA that references an NDA with a REMS with ETASU is received for review,[15] OGD will issue a **REMS Notification Letter** to the ANDA applicant informing them of the requirement for the REMS based on the referenced NDA.
- Prior to approval, FDA will not disclose the existence of an application that is not already publicly disclosed without authorization from the applicant.
- CDER will initiate discussions with the ANDA applicant(s) and the holder of the NDA for the RLD (also referred to as the NDA RLD holder) encourage formation of an

[9] Section 505-1(i)(1)(C)(i) of the FD&C Act.
[10] The term "different, comparable aspect of the elements to assure safe use" is defined as a REMS that uses different methods or operational means than the strategy required for the applicable listed drug, or other application under section 505(j) with the same such listed drug but achieves the same level of safety as such drug. Section 505-1(m).
[11] Section 505-1(i)(1)(C)(ii) of the FD&C Act.
[12] Public Law 112-144.
[13] Generic Drug User Fee Act Program Performance Goals and Procedures, available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf
[14] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022, available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf
See also CDER's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*, available at https://www.fda.gov/media/89061/download
[15] The term "received" means that FDA has made a threshold determination that the ANDA is substantially complete. *See* generally 21 CFR 314.101. This term, while analogous to the term "filed" for new drug applications submitted under section 505(b) of the FD&C Act, will be used throughout this MAPP for consistency of terminology.

Industry Working Group (IWG)[16] for the SSS REMS and to communicate the process and key milestones for development of the SSS REMS.

- CDER will review and act on the proposed SSS REMS or the separate REMS from the ANDA applicant(s), as well as a proposed modification of the NDA RLD REMS (if applicable), according to the relevant actionable dates[17] and timeframes specified in MAPP 4191.1.[18]
    - A REMS Modification will be required from the NDA RLD application holder for the proposed SSS REMS.
    - A **bifurcated REMS** will be requested from the NDA RLD application holder to account for the possibility of tentative approval of the ANDA with the proposed SSS REMS.[19]
- OSE will lead a **CDER Multidisciplinary Review Team**, including representatives from OND, OGD, and other CDER offices, as relevant, in the review of SSS REMS or separate REMS.
- The CDER Multidisciplinary Review Team will discuss issues regarding the proposed SSS REMS or the separate REMS with the REMS Oversight Committee (ROC),[20] as necessary.
- The OSE Project Management Staff will serve as the point of contact (POC) for REMS development communications with the SSS IWG for the SSS REMS or the ANDA applicant/ANDA IWG for the separate REMS. OGD and OND will serve as the POC for

[16] Early in the SSS REMS development process, and to facilitate communication between FDA and the NDA application holder and ANDA applicants, FDA asks the applicant group to designate a single point-of-contact (POC) for their group. This POC could be one of the NDA RLD application holder and ANDA applicants, a third party, or the Drug Master File (DMF) holder.

[17] GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROGRAM ENHANCEMENTS FISCAL YEARS 2018-2022, available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

[18] MAPP 4191.1, *Risk Evaluation and Mitigation Strategies Modifications and Revisions: Responsibilities and Procedures*, available at https://www.fda.gov/media/128782/download

[19] In order for the Agency to approve a single, shared system (as an approvable REMS is required, among other things, to obtain tentative approval) but delay its implementation until the ANDA receives final approval, FDA will request that the NDA RLD application holder submit a REMS modification which proposes a two-part REMS. Part A would consist of the current NDA RLD REMS which applies only to the NDA RLD application holder and would be in effect before the first ANDA receives final approval. Part B would be the single, shared system REMS that would be operational once the first ANDA receives final approval. For more information see Draft *Guidance for Industry: Development of a Shared System REMS*, Section V, C, available at https://www.fda.gov/media/113869/download.

[20] As per current CDER policy all REMS with elements to assure safe use (ETASU), including proposals for new SSS REMS, should be discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the OND, OSE, and ORP.

communications with individual ANDA applicants and the NDA RLD application holder, respectively.

- Decisions regarding the review of SSS REMS or separate REMS will be made in accordance with CDER's policy on equal voice and, if necessary, dispute resolution.[21,22]

RESPONSIBILITIES

The following CDER offices are involved in the development of a SSS REMS and separate REMS: OSE, OGD, OND, OC, OCOMM, and ORP.

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

- Serves as the REMS subject matter expert (SME) on the CDER Multidisciplinary Review Team.
    - Co-chairs, with the OSE Safety Regulatory Project Manager (SRPM), internal CDER Multidisciplinary Review Team meetings.
    - Reviews proposed REMS submissions from the NDA RLD application holder and ANDA applicants and provides content expertise.
    - Prepares the background document and presentation, with input from the CDER Multidisciplinary Review Team, for all ROC meetings to discuss the proposed SSS REMS or separate REMS, if applicable.
    - Drafts language for information requests and comments on the REMS proposals to the NDA RLD application holder and ANDA applicants.
    - Writes and archives the DRM review incorporating the input of the CDER Multidisciplinary Review Team regarding the acceptability of the proposed SSS REMS or separate REMS.
- Facilitates clearance of the draft and final versions of the REMS document.
- Reviews REMS-related language in action letters, if needed.
- Provides final REMS documents to OGD REMS Coordinator and OND SRPM for actions on the ANDA(s) and NDA RLD, respectively.

[21] MAPP 4151.8 *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*, available at https://www.fda.gov/media/79353/download.
[22] MAPP 4151.1 Rev 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain* available at https://www.fda.gov/media/71608/download.

OSE DRM RMA Team Leader (TL)

- Works with the RMA to ensure timely review of the proposed REMS submissions and the final REMS document, REMS materials and REMS supporting document.
- Identifies, with input from DRM Management and other offices, the need to discuss proposed SSS or separate REMS with the ROC.
- Informs CDER Multidisciplinary Review Team (including DRM management and the OGD REMS Coordinator) about progress on reviewing the SSS REMS or separate REMS and whether there are issues that may impact the action date.

OSE DRM Division Director or Designee

- Co-chairs, with the OSE SRPM, meetings[23] with the SSS IWG and ANDA applicant/ANDA IWG**.**

OSE Safety Regulatory Project Manager (SRPM)

- Serves as the POC for communications with ANDA applicants and the NDA RLD application holder for the purposes of developing a SSS REMS or separate REMS after receipt of the **Disclosure Authorization Letter** for one or more ANDA applicants. This includes communicating:
  - questions on proposed SSS REMS or separate REMS,
  - scheduling of meetings to discuss proposed SSS REMS or separate REMS,
  - follow up with the SSS IWG and ANDA applicant/ANDA IWG with inquiries from the Agency, and
  - requests for additional information and comments on the proposed REMS submissions to the SSS IWG and ANDA applicant/ANDA IWG.
- Works with the OGD REMS Coordinator and the OND SRPM for communications with non-responsive ANDA applicants and NDA RLD application holder, respectively.
- Disseminates communications from the SSS IWG and ANDA applicant/ANDA IWG and any other significant issues related to the development of the SSS REMS or separate REMS to the CDER Multidisciplinary Review Team.
- Co-chairs, with the DRM Division Director (or designee) or ORP Assigned Regulatory Counsel, meetings with the SSS IWG and ANDA applicant/ANDA IWG.
- Co-chairs, with the RMA, internal CDER Multidisciplinary Review Team meetings.
- Prepares and submits meeting requests to the ROC to discuss the proposed SSS REMS and separate REMS, as needed.
- Works with DRM staff and other members of the CDER Multidisciplinary Review Team to ensure actionable dates are met.

[23] The ORP Assigned Regulatory Counsel and the OSE SRPM co-chair the kick-off meeting.

- Compiles and maintains the list of the NDA RLD application holder and ANDA applicants for the proposed SSS REMS and/or separate REMS with input from the OGD REMS Coordinator and OND SRPM.

OGD Office of Regulatory Operations (ORO), Division of Filing Review (DFR) Project Manager (PM)

- Notifies the OGD REMS Coordinator Lead in the Office of Bioequivalence that a newly submitted ANDA is required to have a REMS with ETASU and there is no current shared system REMS established.
- Notifies the OGD REMS Coordinator Lead of the filing determination.

OGD Office of Bioequivalence REMS Coordinator Lead (OGD REMS Coordinator Lead)

- Assigns a REMS Coordinator to the newly submitted ANDA required to have a REMS with ETASU.
- Leads and coordinates the oversight of the OGD REMS Coordinator responsibilities.

OGD Office of Bioequivalence REMS Coordinator

- Notifies the relevant CDER offices and groups that an ANDA referencing an NDA RLD with an approved REMS with ETASU has been received for review. Notified groups include:
    - OGD: the OGD ORO Division of Project Management RPM
    - ORP: Assigned Regulatory Counsel
    - OSE: the OSE Consult Box; OSE Chiefs, Project Management Staff (CPMSs); assigned OSE PM (if known); DRM Director and Deputy Director
    - OND: the SRPM and DDS/ADS in the applicable OND review division; Safety Policy Research Team (SPRT), Science Policy Analyst and SRPM
- Sends REMS Notification Letter and Disclosure Authorization Letter template to the ANDA applicant(s).
- Tracks disclosure status of the ANDA applicant(s) and notifies the OSE SRPM when disclosure authorization has been submitted.
- Identifies and keeps track of all approved and pending ANDAs with a REMS requirement referencing the NDA RLD. Provides updates to the OSE SRPM.
- Identifies the appropriate OGD participants for the CDER Multidisciplinary Review Team and provides these names to the OSE SRPM.
- Ensures that the ANDA applicant's REMS submissions are correctly submitted and coded correctly by the document room staff.
- Coordinates the activities (e.g., action dates and approvability of the ANDA) associated with the multidisciplinary review of the ANDA applicant's SSS REMS or separate REMS submissions with the OSE SRPM and the OND SRPM.

- Disseminates REMS development information submitted by the ANDA applicant to their application to the CDER Multidisciplinary Review Team prior to the establishment of the SSS IWG or ANDA applicant/ANDA IWG.[24]
- Disseminates REMS development information and flags notable updates (e.g., updates that may differ from the SSS IWG and ANDA applicant/ANDA IWG development updates) to the CDER Multidisciplinary Review Team that are submitted by the ANDA applicants to their applications.
- Coordinates and communicates with appropriate CDER staff, to ensure actionable dates are met.
- Drafts REMS-related language for ANDA action letters and sends to the DRM RMA for review, if needed.
- Coordinates the action for the SSS REMS with the OGD RPM and OND SRPM to ensure that action letters are issued to all applicable applicants on the same day.

OGD Office of Regulatory Operations, Division of Project Management RPM

- Regularly updates the OGD REMS Coordinator with changes to actionable dates and status of application.
- Drafts ANDA action letters and works with the OGD REMS Coordinator to ensure that action letters are issued to all applicable applicants on the same day.
- Follows MAPP 4520.1, Rev. 2 *Communicating Drug Approval Information* when taking action on an ANDA that approves a new SSS REMS or separate REMS

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

- Oversees the management and coordination of OND review division activities regarding NDA RLD submissions that might have an impact on the development of the SSS REMS or separate REMS.
- Works with the OND SRPM to ensure timely OND division review of and action on NDA RLD submissions related to the proposed SSS REMS or separate REMS.
- Writes and archives a REMS memorandum, when applicable, to document the rationale for modifications to the approved NDA RLD REMS.

OND Safety Regulatory Project Manager (SRPM)

- Identifies the relevant OND participants for the CDER Multidisciplinary Review Team and provides these names to the OSE SRPM.
- Flags the NDA RLD REMS modification submission as a bifurcated REMS in CDER's electronic document archiving system.

[24] The OGD REMS Coordinator provides REMS information to the ANDA applicant until the OSE SRPM POC is introduced as the POC for REMS development communications, typically at the kick-off meeting.

- Works with the document room staff to ensure that the NDA RLD application holder's REMS submissions are correctly coded.
- Determines if there are other open supplements, amendments, assessments and/or other factors related to the NDA RLD that may impact the development of the SSS REMS and informs the OSE SRPM and the CDER Multidisciplinary Review Team.
- Disseminates information and notable updates (e.g., updates that may differ from the SSS IWG and ANDA applicant/ANDA IWG development updates) to the CDER Multidisciplinary Review Team that are submitted by the NDA RLD application holder to their application.
- Works with the OND members of the CDER Multidisciplinary Review Team to ensure timely OND review of and action on the NDA RLD application holder's bifurcated REMS submissions.
- Drafts and facilitates clearance of the NDA RLD action letter and sends to the DRM RMA for review, if needed.
- Coordinates action on the SSS REMS with the OGD REMS Coordinator and OSE SRPM to ensure that action letters are issued to all applicable applicants on the same day.
- Serves as the POC for the NDA RLD application holder regarding proposed modifications of the NDA RLD REMS that are received during, but do not relate to, the development of the SSS REMS.[25]

Office of Compliance (OC) Assigned Consumer Safety Officer

- Provides general compliance advice on SSS REMS and separate REMS development.
- Evaluates the REMS document to assess whether it is written in a manner that is enforceable.
- Assesses timeliness of proposed SSS REMS or separate REMS submissions.
- Assesses the application holder's compliance with the requirements of the REMS program.[26]

Office of Regulatory Policy (ORP) Assigned Regulatory Counsel

- Provides policy advice on SSS REMS and separate REMS development.
- Co-chairs with the OSE SRPM the **kick-off meeting** between the CDER Multidisciplinary Review Team, NDA RLD application holder and ANDA applicants.

[25] See footnote 22

[26] Possible violations include failure to comply with the requirements of the REMS program. See page 25 of the REMS Compliance Program (CP) for a list of the possible REMS violations (i.e., Failure to comply with MG, CP, ETASU A-F, Implementation System, Timetable of Assessments), available at https://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM602307.pdf

- Identifies policy issues that arise during the development of a SSS REMS or separate REMS and prepares policy issue papers for discussion at FDAAA Policy Group, Safety First Steering Committee (SFSC), or ROC meeting as needed.
- Leads regulatory policy discussions, both internal and with the SSS IWG or ANDA applicant/ANDA IWG, that arise during the development of the SSS REMS or separate REMS.
- Identifies issues that arise during the development of a SSS REMS or separate REMS that require legal input from the Office of Chief Counsel (OCC) and acts as liaison between CDER Multidisciplinary Review Team and OCC.

ORP Division of Information Disclosure Policy (DIDP)

- Reviews and redacts the bifurcated REMS document (for SSS REMS) or the separate REMS document and REMS materials and sends them to the Division of Drug Information in the Office of Communications for posting on the FDA's REMS@FDA website.

Office of Communications (OCOMM) Division of Drug Information

- Ensures that the SSS REMS or separate REMS is posted on FDA's REMS@FDA website.

PROCEDURES[27]

1. Initiation of development of a SSS REMS

1.1. The OGD DFR PM will notify the OGD REMS Coordinator Lead when an ANDA referencing an NDA RLD with a REMS with ETASU is submitted to the Agency.

1.2. The OGD DFR PM will follow-up with the OGD REMS Coordinator Lead with a confirmation that the ANDA has been received for review, within 3 business days of the filing determination.

1.3. The OGD REMS Coordinator Lead assigns an OGD REMS Coordinator.

1.4. The assigned OGD REMS Coordinator preliminarily notifies OND (the DDS/ADS, SRPM of the OND Division responsible for the NDA RLD; and SPRT), ORP, and OSE (DRM and SRPM) of the ANDA's submission and follows up with the team once the filing determination is complete. If the ANDA is received, the OGD REMS Coordinator sends a consult request, including relevant actionable dates to the OSE Consult Box within 3 business days of notification that the ANDA is received for review.

[27] Not all tasks occur chronologically; some tasks may occur simultaneously.

1.5. The OND SRPM notifies the CDER Multidisciplinary Review Team if there are any pending REMS modifications or other submissions for the NDA RLD that may potentially affect the development of the SSS REMS.

2. Notification to ANDA applicant of the requirement for REMS with ETASU based on the referenced NDA

2.1. The OGD REMS Coordinator notifies the ANDA applicant that references the NDA RLD of the requirement for a REMS by issuing a REMS Notification Letter with the Disclosure Authorization Letter template within 3 business days of notification that the ANDA is received for review. The OGD REMS Coordinator also sends a copy of the REMS Notification Letter and Disclosure Authorization Letter template to the ANDA applicant via e-mail as a courtesy.

2.2. Within 7 business days of sending the REMS Notification Letter, the OGD REMS Coordinator confirms receipt of the signed Disclosure Authorization Letter from ANDA applicant(s). Within 3 business days of this confirmation, the OGD REMS Coordinator notifies the OSE SRPM that the ANDA applicant submitted the signed Disclosure Authorization Letter.

3. REMS Presubmission Activities

3.1. The OSE SRPM tentatively schedules the "kick-off" meeting with the CDER Multidisciplinary Review Team to be held no later than 60 calendar days after the first ANDA is submitted.

3.2. Within 3 business days of being notified that at least one Disclosure Authorization Letter has been submitted by an ANDA applicant, the OSE SRPM sends a meeting notification inviting the NDA RLD application holder and ANDA applicant(s) to the kick-off meeting to discuss and encourage the development of a SSS REMS. The OSE SRPM sends all meeting materials (standard agenda and FDA attendee list) to the NDA RLD application holder and ANDA applicant(s) and requests the NDA RLD application holder provide teleconference information. The email notification is archived separately in each application.

3.3. The OSE SRPM sends the meeting logistics information to all meeting attendees at least 24 hours prior to the kick-off meeting.[28]

[28] To the extent practical, meeting management follows the principals outlined in the Draft *Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, December 2017. Available at https://www.fda.gov/media/109951/download.

3.4. The ORP Assigned Regulatory Counsel and the OSE SRPM co-chair the kick-off meeting between the CDER Multidisciplinary Review Team, NDA RLD application holder and ANDA applicant(s).

3.5. The OSE SRPM will draft the meeting minutes and circulate them to the CDER Multidisciplinary Review Team for input. The OSE SRPM will then send the minutes for clearance by the ORP Assigned Regulatory Counsel. The OSE SRPM will send the final meeting minutes to each applicant and archive the minutes in each affected application.

3.6. The OSE SRPM will schedule additional meetings with the SSS IWG or ANDA applicant/ANDA IWG as needed.

3.7. The OSE SRPM, the OGD REMS Coordinator, and the OND SRPM will triage and disseminate any updates relevant to the development of the SSS REMS or separate REMS to the CDER Multidisciplinary Review Team as follows:

3.7.1. The OSE SRPM disseminates communications from the SSS IWG and ANDA applicant/ANDA IWG and any other significant issues related to the development of the SSS REMS or separate REMS to the CDER Multidisciplinary Review

3.7.2. The OGD REMS Coordinator disseminates the following information to the CDER Multidisciplinary Review Team:

- REMS development information submitted by the ANDA applicant to their application prior to the establishment of the SSS IWG or ANDA applicant/ANDA IWG.
- REMS development information and notable updates (e.g., updates that may differ from the SSS IWG and ANDA applicant/ANDA IWG development updates) submitted by the ANDA applicant to their application.

3.7.3. The OND SRPM disseminates information and notable updates (e.g., updates that may differ from the SSS IWG and ANDA applicant/ANDA IWG development updates) to the CDER Multidisciplinary Review Team that are submitted by the NDA RLD application holder to their application.

3.8. The OGD REMS Coordinator will notify any subsequent applicants that submit ANDAs that reference the NDA RLD and are received after the kick-off meeting of their requirement for a REMS as described in Section 2.1 above. The OGD REMS Coordinator notifies the CDER Multidisciplinary Review Team of any new ANDAs.

4. CDER Review of Proposed SSS REMS (see Section 5, if a proposed separate REMS has been submitted)

4.1. If the proposed SSS REMS is submitted to the specific applications, the OSE SRPM, the OGD REMS Coordinator, and/or the OND SRPM will notify the CDER

Multidisciplinary Review Team when the proposed SSS REMS has been received from the ANDA applicant(s) and/or the NDA RLD application holder.

4.1.1. If the SSS IWG is using a Drug Master File (DMF) for their submission, OGD, OND, and OSE should follow established procedures[29]

4.2. The OND SRPM verifies that a proposed bifurcated REMS modification has been submitted to the NDA RLD and flags the submission in the CDER electronic document archiving system. If a REMS modification supplement containing the bifurcated REMS has not been received from the NDA RLD application holder within 14 calendar days of receipt of the ANDA(s) proposed SSS REMS submission, the OND SRPM will issue a **REMS Modification Notification letter** to the NDA RLD with the requirement to submit a proposed REMS modification to include the bifurcated REMS.

4.3. The DRM RMA and RMA TL will initiate review of the SSS REMS submission(s) which includes one or more of the following activities in accordance with relevant actionable dates:

4.3.1. Identify specific issues that need broader discussion with the CDER Multidisciplinary Review Team.

4.3.2. Determine if any issues require input from the REMS Oversight Committee (ROC).

4.3.3. Draft interim comments or language for an information request (IR) on the proposed SSS REMS including REMS documents and REMS materials and send it to the OSE SRPM.

4.3.4. Draft written review of the proposed SSS REMS including the rationale for any needed modifications to the currently approved NDA RLD REMS to transition to the SSS REMS.

4.3.5. Identify issues with the proposed SSS REMS (REMS document, REMS materials, and/or REMS supporting document) for discussion with the SSS IWG.

4.3.6. When the DRM Director (or designee) concludes that the proposed SSS REMS is acceptable, send the bifurcated REMS document and any attestations for pre-clearance to the ORP Assigned Regulatory Counsel.

[29] See Draft *Guidance for Industry: Use of a Drug Master File for Shared System REMS Submissions*, available at https://www.fda.gov/media/109124/download and the Guideline for Drug Master Files (DMF), available at https://www.fda.gov/drugs/drug-master-files-dmfs/guideline-drug-master-files-dmf

4.4. The DRM RMA or RMA TL will contact the OSE SRPM to schedule any internal meetings with the CDER Multidisciplinary Review team or meetings with the SSS IWG.

4.5. The OSE SRPM will:

4.5.1. Provide FDA comments or an IR to the SSS IWG based on CDER Multidisciplinary Review Team evaluation.

4.5.2. Coordinate with the OGD REMS Coordinator prior to issuing the comments/IR to ensure the dates and issuance of an IR aligns with each respective ANDA(s) review timeline.

4.5.3. Notify the OGD REMS Coordinator and OND SRPM that the comments/IR have been sent.

4.5.4. Archive the communications in the DMF or in the CDER electronic document archiving system for individual applications as appropriate.

4.6. The OSE SRPM will, if the CDER Multidisciplinary Review Team finds the proposed SSS REMS acceptable, instruct the applicant(s) to submit the final, agreed-upon SSS REMS as an amendment to their applications.

4.7. The DRM RMA will review the final, agreed-upon SSS REMS to ensure the submission is complete and acceptable and upload their final review in the CDER electronic document archiving system.

4.8. The CDER Multidisciplinary Review Team will discuss whether OCOMM should be consulted.

5. CDER Review of Proposed Separate REMS

5.1. If a proposed separate REMS is submitted to the specific ANDA(s), the OGD REMS Coordinator will notify the OSE SRPM and the ORP Assigned Regulatory Counsel by email that it has been received from the ANDA applicant(s).

5.1.1. If the ANDA IWG is using a DMF for their submission, OGD and OSE should follow established procedures.

5.2. The DRM RMA and RMA TL will initiate review of the separate REMS submission(s) which includes one or more of the following activities in accordance with relevant actionable dates:

5.2.1. Identify specific issues that need broader discussion with the CDER Multidisciplinary Review Team.

5.2.2. Determine if any issues require input from the ROC.

5.2.3. Draft interim comments or language for an IR on the proposed separate REMS including REMS documents and REMS materials and send to the OSE SRPM.

5.2.4. Draft written review of the proposed separate REMS including an analysis of the comparability of the proposed separate REMS to the approved NDA

RLD REMS and any potential modifications that might be required of the NDA RLD REMS to accommodate the separate REMS.

5.2.5. Identify issues with the proposed separate REMS (REMS document, REMS materials, and/or REMS supporting document) for discussion with the ANDA applicant/ANDA IWG.

5.2.6. When the DRM Director (or designee) concludes that the proposed separate REMS acceptable, send the REMS document and any attestations for pre-clearance to the ORP Assigned Regulatory Counsel.

5.3. The DRM RMA or RMA TL will contact the OSE SRPM to schedule any internal meetings with the CDER Multidisciplinary Review Team or meetings with the ANDA applicant/ANDA IWG.

5.4. The OSE SRPM will:

5.4.1. Provide FDA comments or an IR to the ANDA applicant/ANDA IWG by email based on CDER Multidisciplinary Review Team evaluation.

5.4.2. Coordinate with the OGD REMS Coordinator prior to issuing the comments/IR to ensure the dates and issuance of an IR aligns with each respective ANDA(s) review timeline.

5.4.3. Notify the OGD REMS Coordinator that the comments/IR have been sent

5.4.4. Archive the communications in the DMF or in the CDER electronic document archiving system for individual applications as appropriate.

5.5. The OSE SRPM will, if the CDER Multidisciplinary Review Team finds the proposed separate REMS acceptable, instruct the ANDA applicant/ANDA IWG to submit the final, agreed-upon separate REMS as an amendment to their applications.

5.6. The DRM RMA will review the final, agreed-upon separate REMS to ensure the submission is complete and acceptable and upload their review in the CDER electronic document archiving system.

5.7. The CDER Multidisciplinary Review Team will discuss whether OCOMM should be consulted.

6. Approval of the SSS REMS or Separate REMS with Final or Tentative Approval of the ANDA(s)

6.1. If the final, agreed-upon SSS REMS or separate REMS is complete and acceptable, and the ANDA is otherwise going to receive approval or tentative approval, the OGD REMS Coordinator will draft the appropriate REMS language for the ANDA action letter(s) and send to Safety Requirements Team (SRT) for clearance.

6.2. For a SSS REMS, if an ANDA is going to receive either final or tentative approval, the OND SRPM will draft the supplement approval letter (REMS modification) for the NDA RLD and send this letter to SRT for clearance.

6.2.1. The OND SRPM will work with the CDER Multidisciplinary Review Team to determine if the NDA RLD application holder should submit revised labeling to align with the approved SSS REMS.

6.3. If the determination has been made that modification of the NDA RLD is necessary to accommodate a separate REMS, then the OND SRPM will draft a REMS Modification Notification Letter to the NDA RLD applicant and send this letter to SRT for clearance.

6.4. The OGD REMS Coordinator will notify the OSE SRPM and OND SRPM of the approval or tentative approval action for an ANDA.

6.5. On the same day that the ANDA receives final approval, the OND SRPM will request a labeling supplement from the NDA RLD application holder to revise product labeling to align with the approved SSS REMS (if applicable) within 30 calendar days.

6.6. The OND SRPM and OGD REMS Coordinator will ensure that the letters approving or tentatively approving the ANDA that approves the SSS REMS and approving the NDA RLD bifurcated REMS supplement, are issued on the same day.

6.7. When a separate REMS is approved and modification of the NDA RLD is necessary to accommodate the separate REMS, the OND SRPM will ensure the REMS Modification Notification letter is issued to the NDA RLD on the same day the separate REMS is approved.

6.7.1. The OGD Office of Regulatory Operations, Division of Project Management RPM follows MAPP 4520.1, Rev. 2 when taking action on an ANDA that approves a new SSS REMS or separate REMS.

6.8. ORP DIDP receives the bifurcated REMS document (for SSS REMS) or the separate REMS document and REMS materials:

6.8.1. For SSS REMS for the NDA RLD REMS: DIDP receives the approval letter for the bifurcated REMS modification supplement (with the attached bifurcated REMS document and REMS materials) through CDER's electronic document archiving system.

6.8.2. For separate REMS for ANDAs receiving final approval: DIDP receives the separate REMS document and REMS materials from the OGD REMS Coordinator.

6.9. ORP DIDP redacts the aforementioned REMS-related documents and places the SSS REMS or separate REMS document and appended materials in an electronic folder for access by the OCOMM Division of Drug Information.

6.10. The OCOMM Division of Drug Information will ensure the following is posted on the FDA's REMS@FDA website within 3 business days of approval:

6.10.1. SSS REMS or separate REMS if ANDAs are receiving a final approval

6.10.2. Part A of the NDA RLD Bifurcated REMS if the ANDAs are receiving tentative approval.

7. Approval of the SSS REMS or Separate REMS with Final Approval for ANDA that initially received Tentative Approval

7.1. The OGD Division of Project Management RPM will notify the REMS Coordinator when a first ANDA that was previously Tentatively Approved, submits a request for Full Approval and provide the relevant actionable date.

7.2. The OGD REMS Coordinator will contact the OSE SRPM and DRM to confirm if the SSS REMS or separate REMS is still acceptable from the issuance of the Tentative Approval.

7.2.1. If the SSS REMS or separate REMS is still acceptable and will remain acceptable until the ANDA's actionable date; no additional steps for review of the SSS REMS or separate REMS is necessary, proceed with next steps beginning with 7.6.

7.2.2. If the SSS REMS or separate REMS is no longer acceptable or not expected to remain acceptable through the ANDA's actionable date, proceed with a review of the SSS REMS or separate REMS, beginning with 7.3.

7.3. Within 3 business days of the notification outlined in 7.1, the OGD REMS Coordinator sends a consult, including relevant actionable dates to the OSE Consult Box (CDER-OSE-CONSULTS).

7.4. Within 7 business days of the notification outlined in 7.1:

7.4.1 If the ANDA applicant is using a DMF for their submission, the OGD REMS Coordinator should follow established procedures.

7.4.2 If the ANDA applicant is not using the DMF for their submission, the OGD REMS Coordinator sends an information request to the applicant, requesting that an updated version of the SSS REMS or separate REMS be submitted to the application.

7.5. Review of the SSS REMS or separate REMS will follow the applicable processes outlined in sections 4 and 5 above.

7.6. The OGD REMS Coordinator will draft the appropriate REMS language for the ANDA action letter and send to SRT for clearance. If the ANDA is receiving a Complete Response, the action letter is not cleared by SRT.

7.7. The OGD REMS Coordinator will notify the OSE SRPM and OND SRPM of the approval action for an ANDA(s).

7.8. On the same day that the ANDA receives final approval, the OND SRPM will request a labeling supplement from the NDA RLD application holder to revise product labeling to align with the approved SSS REMS (if applicable) within 30 calendar days.

7.9. ORP DIDP receives the SSS REMS or the separate REMS document and REMS materials from OGD REMS Coordinator or the OGD Division of Project Management RPM.

7.10. ORP DIDP redacts the aforementioned REMS-related documents and places the SSS REMS or separate REMS document and appended materials in an electronic folder for access by the OCOMM Division of Drug Information.

7.11. The OCOMM Division of Drug Information will post the SSS REMS or separate REMS on the FDA's REMS@FDA website within 3 business days of approval.

REFERENCES

1. Draft Guidance for Industry: Development of a Shared System REMS, available at https://www.fda.gov/media/113869/download.
2. MAPP 4191.1 Risk Evaluation and Mitigation Strategies (REMS) Modifications and Revision, available at https://www.fda.gov/media/128782/download.
3. MAPP 4151.8 Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions, available at https://www.fda.gov/media/79353/download.
4. MAPP 4151.1 Rev 1 Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain, available at https://www.fda.gov/media/71608/download.
5. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, available at https://www.fda.gov/media/109951/download.

6. Draft Guidance for Industry: Use of a Drug Master File for Shared System REMS Submissions, available at https://www.fda.gov/media/109124/download.
7. Guidance for Industry: Risk Evaluation and Mitigation Strategies: Modifications and Revisions, available at https://www.fda.gov/media/128651/download.
8. MAPP 4520.1 Rev.2 Communicating Drug Approval Information, available at https://www.fda.gov/media/72544/download.

DEFINITIONS

ANDA Applicant/ANDA IWG - refers to a single ANDA applicant or the working group that more than one ANDA applicants have formed to develop the separate REMS.

Bifurcated REMS - A two-part REMS consisting of Part A and Part B that is submitted by the NDA applicant as a REMS modification in response to FDA's request. Part A consists of the NDA RLD REMS which applies only to the NDA RLD application holder and would be in effect when the first ANDA receives tentative approval. Part B consists of the single, shared system REMS that would be operational once the first ANDA receives final approval.

CDER Multidisciplinary Review Team – consists of the following individuals (at a minimum): DRM RMA and RMA TL, OSE SRPM, OND DDS/ADS and OND SRPM, OGD REMS Coordinator, ORP Assigned Regulatory Counsel, and OC Assigned Consumer Safety Officer.

Disclosure Authorization Letter –a letter that applicants complete using a CDER letter template and send to the Agency that allows the Agency to hold meetings between multiple applicants.

Kick-Off Meeting – a meeting that is held between the CDER Multidisciplinary Review Team, NDA RLD application holder and ANDA applicants(s) to discuss the applicable processes and to set forth FDA expectations including the designation of a single POC[30] for the SSS IWG or ANDA applicant/ANDA IWG, timelines for reaching agreement on a shared governance, and timelines for submission of the proposed SSS REMS or a separate REMS. It will generally occur within 60 calendar days of the first ANDA's submission date.

REMS Modification Notification Letter [for the purpose of this MAPP] – this letter informs NDA applicants how they must modify their REMS to accommodate different, comparable aspects of the elements to assure safe use for a drug that is subject of an application under section 505(j), and the applicable listed drug.

REMS Notification Letter [for ANDA applicants] **–** The letter informs ANDA applicant(s) that the REMS for [APPLICABLE LISTED DRUG] includes ETASU and that the ANDA may use a single, shared system (SSS) with the listed drug it references for the ETASU or a different, comparable aspect of the ETASU. The letter provides contact information for NDA RLD REMS industry contact. The REMS Notification Letter is signed by the Director (or designee) of the Office of Bioequivalence.

Single, Shared System (SSS) REMS - REMS that include ETASU and at least one ANDA product and its reference listed drug.

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

Separate REMS [for the purposes of this document] **–** the ANDA applicant/ANDA IWG proposed separate REMS. The separate REMS must use an aspect of the ETASU that is comparable to that of the NDA RLD REMS and achieves the same level of safety.

Point of Contact (POC) – the designated point-of-contact 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 about the status of developing the shared system.

Industry Working Group (IWG) – refers to the working group that the applicants have formed to develop the SSS or separate REMS. Some applicants have used an IWG to facilitate negotiations and agreements among the applicants to develop a shared system REMS on issues such as confidentiality, governance, voting structure, cost-sharing, any potential changes to the drug distribution model, and any other issues that may come up during the collaboration.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
10/28/20	1	MAPP was revised to account for REMS statutory revisions included in the CREATES Act of 2019/Appropriations Act for 2020.

[30] Early in the SSS REMS development process, and to facilitate communication between FDA and the NDA application holder and ANDA applicants, FDA asks the applicant group to designate a **single point-of-contact (POC)** for their group. This POC could be one of the NDA RLD application holder and ANDA applicants, a third party, or the DMF holder.