Use of a Drug Master File for Shared System REMS Submissions

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Gita Toyserkani 301-796-1783 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for applicants that are part of a shared system risk evaluation and mitigation strategy (REMS) on using an electronic Type V[2] Drug Master File (DMF)[3] for shared system REMS (SSR) submissions. The recommendations in this guidance are intended to improve the efficiency of submitting SSR to the Agency.[4]

The use of a DMF is not a requirement for SSRs. However, if applicants that are subject to and participating in an SSR choose to use a DMF, this guidance provides an overview of a recommended approach for their SSR submissions. Additional and more-detailed submission instructions are included in a separate technical guide, *Technical Conformance Guide for Shared System REMS Drug Master File Submissions (the SSR DMF Technical Conformance Guide),* which will be updated periodically.[5]

[1] This guidance has been prepared by the Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology, in collaboration with other Offices in the Center for Drug Evaluation and Research and with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

[2] Type V FDA-Accepted Reference Information DMF.

[3] 21 CFR 314.420(a)(5).

[4] This guidance discusses DMF submissions for the following products: drug products marketed for human use with approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs), and biological products marketed for human use with approved biologics license applications (BLAs).

[5] To make sure you have the most recent version of the SSR DMF Technical Conformance Guide, check the FDA website at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm.

If SSR applicants choose to use the DMF, as of the date specified by FDA, they must submit the DMFs in the Electronic Common Technical Document (eCTD) format, as previously stated in the guidance for industry on *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Revision 4).*[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A REMS is a required risk management plan that uses tools beyond the FDA-approved prescribing information to ensure that the benefits of certain drugs[7] outweigh their risks.[8] FDA can, under certain circumstances,[9] require that the REMS for a drug include one or more elements to assure safe use (ETASU).[10] When ETASUs are required for an innovator drug, any abbreviated new drug application (ANDA)[11] referencing that innovator drug must use an SSR with the innovator (unless FDA waives the requirement for using a shared system).[12] There are also circumstances under which multiple applicants form an SSR to minimize the burden on the health care delivery system, such as for a class of similar products.

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[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or the FDA Biologics guidance web page at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryinformation/Guidances/default.htm.

[7] For the purpose of this guidance, unless otherwise specified, references to *drugs* include drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b) or (j)) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262)), other than biological products that also meet the definition of a *device* in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[8] Section 505-1 of the FD&C Act (21 U.S.C. 355-1), as amended by the Food and Drug Administration Amendments Act of 2007.

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

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

[11] *Abbreviated new drug application (ANDA)* refers to an application submitted or approved under section 505(j) of the FD&C Act.

[12] Section 505-1(i)(1)(B) of the FD&C Act.

A DMF is a voluntary submission that may be used to provide confidential detailed information to the Agency.[13] The DMF holder may authorize other applicants to reference information in the holder's DMF. A DMF is submitted solely at the discretion of the DMF holder, and the technical contents of a DMF are customarily reviewed by FDA only in connection with the review of an application. There are several types of DMFs; a Type V is used for "FDA-accepted reference information."[14]

As part of an SSR, multiple applicants need to coordinate the submission of identical REMS-related documents by each applicant to its own application. To improve the efficiency of the submission and review process for SSRs, FDA recommends that applicants use a Type V DMF for their SSR submissions. As noted above, as of the date specified by FDA, applicants who choose to use a Type V DMF for an SSR must make the DMF submissions electronically, as required in the binding guidance for industry on *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Revision 4).*

In addition to the recommendations provided in this guidance, FDA advises stakeholders to refer to other relevant FDA resources to help create their submissions, such as the following:

- *Technical Conformance Guide for Shared System REMS Drug Master File Submissions*[15]
- *Guideline for Drug Master Files*[16]
- FDA's DMF web page[17]
- Draft guidance for industry *Format and Content of a REMS Document*[18]

[13] Confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs (see *Guideline for Drug Master Files*, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm).

[14] 21 CFR 314.420(a)(5).

[15] SSR DMF Technical Conformance Guide is available at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm.

[16] Available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm.

[17] See the FDA DMF web page for additional DMF information including various letter templates (e.g., letter of authorization), at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm. and at https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/newdrugapplicationndaprocess/ucm211604.htm.

[18] When final, this guidance will represent FDA's current thinking on this topic.

- Guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*

III. OVERVIEW OF THE SSR DMF

This section provides an overview of how a Type V DMF can be used for an SSR (SSR DMF). Detailed submission instructions for each type of REMS submission or cross-reference submission to the SSR DMF (e.g., minor REMS modification, REMS assessment) are provided in the *SSR DMF Technical Conformance Guide*, which will be updated periodically.[19]

A. Ownership of the SSR DMF

The owner of the SSR DMF is the DMF holder who is jointly designated by the SSR applicants. Only one company should be listed as the DMF holder. The DMF holder will make submissions to the DMF on behalf of the SSR applicants. Therefore, FDA will consider any submission to the SSR DMF to represent the views of the participating SSR applicants.

B. Establishing the SSR DMF

As with any Type V DMF, the DMF holder must submit a letter of intent to the FDA DMF staff at dmfquestion@fda.hhs.gov to request preclearance.[20] The letter should include the name of the FDA project manager who has been assigned as the point-of-contact for the SSR in addition to the necessary information that should be included in the request.[21]

The DMF holder should also request from FDA a pre-assigned DMF number for the new DMF.[22] Once the number is obtained, the DMF holder should submit a "DMF Original" submission containing a cover letter and complete administrative and technical information (e.g.,

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[19] See footnote 15.

[20] 21 CFR 314.420(a)(5).

[21] See https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm.

[22] See https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm). See CBER SOPP 8117: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109641.htm.

the SSR submission that is the subject of the DMF) in the appropriate sections of the eCTD format.[23]

C. Authorization To Refer to the SSR DMF

The DMF holder must submit letters of authorization (LOAs) to the DMF that permit FDA to review information in the DMF in support of the SSR applicants' applications.[24] The DMF holder should submit a separate LOA to the DMF for each SSR applicant. If an SSR applicant is also the DMF holder, an LOA should still be submitted to the DMF. The DMF holder does not need to submit a new LOA for each new submission to the DMF unless there is a change in the DMF holder name or the authorized party name.

The DMF holder should also send a copy of the LOA to each SSR applicant who has been authorized to incorporate the information contained in the DMF by reference. Each SSR applicant should then submit the copy of the LOA to its own application.[25] SSR applicants only need to submit this LOA to their application one time unless there is a change in the DMF holder name or the authorized party name.

D. Contents of the SSR DMF

In general, only information related to the SSR should be submitted, through the DMF holder, to the SSR DMF. Information that is application-specific should be submitted by an applicant to its own individual application.

Items that ***should*** be submitted to the SSR DMF include, but are not limited to, the following:

- The REMS Document[26]
- The REMS Materials
- The REMS Supporting Document

[23] See section IV.B. Administrative Information of the *Guideline for Drug Master Files*, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm.

[24] 21 CFR 314.420(b); see also section V.A. Letter of Authorization to FDA of the *Guideline for Drug Master Files*, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm.

[25] See section V.B Copy to Applicant, Sponsor, or Other Holder of the *Guideline for Drug Master Files*, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm.

[26] See draft guidance for industry *Format and Content of a REMS Document.* When final, this guidance will represent FDA's current thinking on this topic.

- REMS Assessment Methodologies and REMS Assessments[27]
- REMS Correspondence
- REMS History
- Any interim versions of documents that need FDA's review
- Any responses to FDA requests for information concerning the SSR
- Documents that are submitted to all DMFs, such as the DMF Amendments and LOAs

Items that ***should not*** be submitted to the SSR DMF (and instead should be submitted to each applicant's individual application) include, but are not limited to, the following:

- Labeling, including Medication Guides that are part of a REMS (See section IV of this document, *Cross-Reference Submissions for SSR Applicants*)
- Product-specific information, such as REMS Assessment Adverse Event summaries[28]
- REMS changes[29] that apply to only one application in the SSR (e.g., efficacy supplement for new indication for use)

E. Communication About the SSR DMF

FDA will contact the DMF holder regarding DMF technical issues and questions about the administrative content (e.g., information in eCTD section 1.4). FDA will contact the SSR applicants' designated point-of-contact[30] with questions about the REMS content in the DMF (e.g., information in eCTD section 1.16). It is up to the SSR applicants to decide who else, if anyone, should be involved in each of these types of discussions.

IV. CROSS-REFERENCE SUBMISSIONS FOR SSR APPLICANTS

[27] FDA may ask applicants to submit product-specific adverse event summaries as part of a REMS assessment. These product-specific summaries should be submitted to each applicant's individual application, and not to the SSR DMF.

[28] See footnote 27.

[29] See guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*.

[30] Early in the SSR development process, and to facilitate communication between FDA and the SSR applicants, FDA asks the SSR applicant group to designate a single point-of-contact for their group.

For the purposes of this guidance, a *cross-reference submission* is the submission that an SSR applicant will make to its individual application to incorporate by reference information that the DMF holder has submitted to the SSR DMF.[31]

This section provides a brief overview of cross-reference submissions.

- A cross-reference submission ***will*** be needed after any of the following has been submitted to the SSR DMF:
    - REMS Original
    - Minor REMS Modification
    - Major REMS Modification
    - REMS Modification Due to Safety Label Changes
    - REMS Revision
    - REMS Assessment[32]

  The cross-reference submission for a REMS Original,[33] minor REMS modification, major REMS modification, and REMS modification due to safety label changes should be submitted to the individual application as an amendment, if applicable, or a supplement. Submissions of REMS revisions[34] and REMS assessments are not supplemental applications. Therefore, the cross-reference submissions should also not be submitted as supplements.

[31] The cross-reference submission serves to "incorporate the material in the DMF by reference." See section VI.B of the *Guideline for Drug Master Files*, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm.

[32] To the extent that REMS Assessments are not required for ANDAs, a cross-reference submission for REMS Assessments is also not required; see section 505-1(g) of the FD&C Act.

[33] If the *REMS Original* submission is part of the Original Application, the cross-reference submission will be an amendment to a pending application.

[34] See guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*.

- A cross-reference submission ***will not*** be needed after the following have been submitted to the SSR DMF:
    - REMS Assessment Methodology
    - REMS Correspondence
    - Interim versions of REMS documents, REMS materials, or REMS supporting documents
    - Responses to FDA Requests for Information

- In most cases, the cross-reference submission will only include a cover letter, Form FDA 356h, and, as applicable, a Medication Guide.[35]

- An SSR applicant should submit a copy of the DMF holder's LOA to its application either before or at the time of the applicant's first cross-reference submission. As previously described in section III.C *Authorization To Refer to the SSR DMF*, the SSR applicant should submit this LOA only once, unless there is a change in the DMF holder name or the authorized party name.

- To facilitate tracking of the cross-reference submissions, FDA recommends that SSR applicants submit their cross-reference submissions as soon as possible after the DMF holder has made the corresponding submission to the SSR DMF. In addition, FDA recommends that SSR applicants work together to make their cross-reference submissions on the same day.

V. CONTACT INFORMATION

For questions about providing electronic submissions according to the recommendations in this guidance, you should contact FDA's REMS Team at REMS@fda.hhs.gov for CDER products, and contact Review Management at ESUBPREP@fda.hhs.gov for CBER products. Specific questions about the content of applications should be directed to the appropriate review division or office.

[35] Medication Guides that are part of a REMS should be included in each applicant's cross-reference submission to its NDA/BLA/ANDA. Please note that if changes have been made to the Medication Guide that is part of a REMS, a REMS supplement should be submitted to the application, as well as a cross reference to the DMF. If a product has a Medication Guide that is not part of the REMS, it does not need to be included in any REMS submission.