Technical Conformance Guide for Shared System REMS Drug Master File Submissions (the SSR DMF Technical Conformance Guide)

Version 1: November 2017

Contents

SSR DMF Technical Conformance Guide

1 Introduction

1.1 Background

This Technical Conformance Guide (Guide) provides specifications, recommendations, and general considerations on how to submit Risk Evaluation and Mitigation Strategy (REMS) submissions to a Type V[1] Drug Master File (DMF) that is being used for a Shared System REMS (SSR) (an SSR DMF) and how to submit the corresponding cross-reference submission. This Guide supplements the guidance for industry *Use of a Drug Master File for Shared System REMS Submissions.*[2]

1.2 Purpose

This Guide provides technical recommendations to holders of applications that are part of Shared System REMS (SSR applicants) for REMS submissions to an SSR DMF and for the corresponding cross-reference submissions to applicants' individual applications. The Guide is intended to complement and promote interactions between applicants and the Food and Drug Administration (FDA). However, it is not intended to replace the need for applicants to communicate directly with review divisions regarding implementation approaches or issues relating to their individual application. The use of an SSR DMF is expected to improve the efficiency of the submission and review process for SSR.

1.3 Document Revision and Control

FDA intends to issue an initial *Federal Register* notice announcing availability of this Guide and seeking public comment on its contents. Future revisions will be posted directly on the eCTD Resources Web page [3] and the revision history page of this document will contain sufficient information to indicate which sections of the Guide have been revised.

---

[1] Type V FDA-Accepted Reference Information DMF

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

[3] Available at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm.

1.4 Relationship to Other Documents

This Guide supplements the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions.*[4] In addition, applicants should reference the following:

- *Guideline for Drug Master Files*[5]
- FDA DMF web page[6]
- Guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Revision 4)*[7]
- Draft guidance for industry *Format and Content of a REMS Document*[8]
- Guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* [9]

FDA requests that a DMF holder adhere to the obligations and commitments for Type V DMFs (as described in the references above) as well as the specific recommendations outlined in this document for DMFs that are being used for SSR.

1.5 Document Organization

This Guide contains instructions that are specific to the DMF holder as well as instructions that are specific to individual SSR applicants.

The document is organized as follows:

Section 2:	General instructions for a DMF holder on REMS submissions to the SSR DMF
Section 3:	General instructions for SSR applicants on submissions to cross-reference a REMS submission to the SSR DMF

[4] Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM580181.pdf.

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

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

[7] Available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

[8] When final, this guidance will represent FDA's current thinking on this topic, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.

[9] Available at .http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm441226.pdf.

Appendices: Detailed submission instructions and letter templates

2 General Instructions for REMS Submissions to the SSR DMF

This section provides general instructions that apply to all types of REMS submissions to the SSR DMF, including:

- REMS Original[10]
- Minor REMS Modification
- Major REMS Modification
- REMS Modifications due to Safety Labeling Changes
- REMS Revision
- REMS Assessment
- REMS Assessment Methodology
- REMS Correspondence

Instructions that are specific to a particular type of REMS submission are described in *Appendix A.*

Historical REMS Content

If the SSR DMF is being established for an "approved SSR," FDA may ask that the DMF be prepopulated with some select, historical REMS submissions (e.g., previously approved versions of the REMS or past REMS assessments). FDA will provide instructions on what, if any, historical content should be submitted to the SSR DMF and how to submit it. Note that historical content should be submitted to the SSR DMF prior to submitting any new REMS submissions (e.g., proposed minor REMS modification).

2.1 Electronic Submissions to the DMF

As of the date specified by FDA, submissions to the DMF must be electronic, in the Electronic Common Technical Document (eCTD) format, per 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)*[11] and as noted in the guidance on *Use of a Drug Master File for Shared System REMS Submissions.* Electronic submission will improve review efficiency because the eCTD backbone is able to keep track of the latest versions of each document submitted, minimizing the need for duplicate submissions and re-review.

To take advantage of the lifecycle design features that are available when using the eCTD format, and to minimize confusion, the following are critical:

[10] Refers to a REMS for which FDA has never issued an approval letter (a new, proposed REMS).

[11] See pages 3-4 of the guidance, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf. See also FDA's eCTD web page at https://www.fda.gov/ectd.

- Apply the correct operation attribute values. If a document replaces a document previously submitted with an eCTD backbone file within the same application, please use the eCTD *replace* operation to indicate this, rather than submitting the file as new. Please do not indicate that files are new if they are in fact replacing files already submitted. If you intend to remove a file, please use the *delete* operation.[7]

- Retain the leaf title used for a particular document for the lifecycle of that document.

- Use consistent leaf titles for the same type of document.

2.2 REMS Submission Contents and Placement in the eCTD

All REMS submissions to the DMF should include the following documents, under the following eCTD sections in Module 1 under the appropriate subheadings[12]:

Document/Information	eCTD Section
Cover Letter	*1.2 Cover Letters*
Statement of Commitment	*1.2 Cover Letters*
Administrative Information	*1.3 Administrative Information*
REMS-related content	*1.16 Risk Management Plans*

[12] See The Comprehensive Table of Contents Headings and Hierarchy at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf.

2.3 Creating Subheadings Using Leaf Titles

If you are using the eCTD Backbone Files Specification for Module 1 version 1.3 (DTD v2.01), follow the naming convention directions below to create subheadings using leaf titles.[13] To differentiate files under the common 1.16 heading, begin the leaf title with the appropriate "leaf title subheading." The format is included below:

Format: [Leaf title subheading] **[Leaf title]**

Example: [Draft] **[Supporting Document]** ➔ Draft Supporting Document

For REMS Original, all types of REMS Modifications, and REMS Revision Submissions, leaf title subheadings should be used for the REMS document[14], all REMS materials, and the REMS supporting document. There are other documents in these submission types, such as the reviewer guide, that do not need leaf title subheadings.

Table 1 contains general information on the leaf title subheading conventions for each submission type.

Table 1: Leaf Title Subheadings and Leaf Titles

Type of Submission	Leaf title subheadings	Leaf title
REMS Original	Draft Final	If possible, the leaf title should match the document name and/or contain information about the content of the document. [15] Specific instructions are included in *Appendix A*.
REMS Revision	Draft (with track changes) Final	
REMS Modification: • Minor REMS Modification • Major REMS Modification • REMS Modifications Due to Safety Labeling Changes	Draft Final	

[13] If you are using the eCTD Backbone Files Specification for Module 1 Version 2.3 (DTD v3.3), you do not need to create leaf title subheadings since REMS Heading 1.16 includes subheadings. See https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm535180.htm.

[14] See draft guidance for industry *Format and Content of a REMS Document*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.

[15] Leaf titles for eCTDs are displayed to the reviewer when viewing an eCTD application. Although some eCTD tools generate leaf titles that are similar to file names, the two are not related. All modules of the eCTD should contain descriptive eCTD leaf titles that are short, meaningful, and indicative of each document's content. You should not include the eCTD section number in the leaf title.

Type of Submission	Leaf title subheadings	Leaf title
REMS Assessment	Assessment	
REMS Assessment Methodology (e.g., Survey)	Methodology Survey Methodology Other	
REMS Correspondence	Correspondence	

2.4 File Names

Files submitted to the DMF should use meaningful file names that are indicative of the file's contents, and that will allow the reviewer to easily identify files. A suggested file naming format is included below:

a. **Format:** [*stakeholder*] **[form or document type]**
   Examples: [*prescriber*] **[letter]** ➔ prescriber-letter
   [*pharmacy*] **[enrollment form]** ➔ pharmacy-enrollment-form

b. A stakeholder does not need to be specified for documents that are targeted to multiple stakeholders (e.g., REMS Web site = web site).

c. If a document contains track changes or annotations, this should be reflected in the file name and leaf title. For example: prescriber letter-tracked.

Examples of suggested file names are included in *Appendix C*.

2.5 File Formats

Submissions to the DMF may contain Word and/or PDF documents. See Table 2.5 below.

Table 2: File Formats

Type of REMS Submission	File format(s)
REMS Original	Word and PDF
REMS Modification (all types)	Word and PDF
REMS Revision	Word and PDF
REMS Assessment	PDF
REMS Assessment Methodology (e.g., survey, analysis of claims data)	Survey methodology = Word Other methodology = PDF
REMS Correspondence	PDF for most submissions

a. **PDF:** PDFs should conform to the current PDF Specifications[16] with regard to hyperlinks, table of contents, and bookmarks.

b. **Word:** Word is the file format that is used to submit individual versions of each document in the REMS. We are aware that some REMS documents, such as Web site mock-ups, are not created in Word. Therefore, it is acceptable to submit these documents in PDF. However, if extensive revisions are required, FDA may ask that the text of these documents be provided in Word format.

2.6 Cover Letter

All submissions to the DMF should include a cover letter with a submission description and table of contents. A cover letter template is included in *Appendix B*; the template shows the information that needs to be provided for each submission to the DMF, so that the submission can be tracked, routed, and reviewed appropriately.

Submission Category(ies)

Submission category should be included in all cover letters. The submission category helps ensure that the submission is appropriately tracked, routed, and reviewed.

The cover letter template includes a field called, "Submission Categories." Instructions on what to include in this field, for each type of REMS submission, are included in *Appendix B*.

16 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf.

Cover Letter Leaf Titles

The leaf title for cover letters should also contain information about the contents of the submission. The general format for cover letter leaf titles and an example are included below.

> **General Format: Cover Letter** [Sequence No.] **[Date YYYYMMDD]** [Submission information*]
>
> **Example:** Cover Letter 0006 **20130618** Assessment 2 at 12 months
>
> ***** Depending on the submission type, the [Submission information] section, may include additional details

2.7 REMS History

The REMS history provides a summary of all changes to the REMS since approval and all REMS assessments to date. It should be submitted with REMS assessments and with each submission that proposes changes to the REMS (revisions, minor modifications, major modifications, and modifications due to safety labeling changes). The REMS history can be included in the cover letter or submitted as a single PDF file. The instructions for submitting the REMS history as a single PDF file are included in Appendix A.

The REMS history should be similar in format to the summary that application holders include in labeling supplements that provides the history of changes made to the product labeling. The REMS history should be in tabular format and should contain the REMS assessment number or the type of REMS change. The REMS history should also contain a brief overview of the revisions or modifications, list the REMS materials affected, and, in the case of REMS modifications, provide either the date of submission (for REMS revisions and pending modifications) or approval.

Example REMS History:

Assessment No. or [Type of REMS change]	Date Submitted to SSR DMF [Seq. No.]	Date Approved	Document(s) Affected	Overview of Changes
Original	01/01/2015 [0001]	10/02/2015	Original REMS	N/A
[Major Mod]	02/22/2016 [0003]	08/08/2016	• REMS Document • Prescriber Enrollment Form • FAQ • Supporting Document	Changed to address the addition of permanent AF to the Contraindications Section of the Prescribing Information
Assessment 1 @ 6 months	04/02/2016 [0005]	N/A	N/A	N/A
[Revision]	12/06/2016 [0007]	N/A	Prescriber Brochure	Fixed punctuation

Assessment No. or [Type of REMS change]	Date Submitted to SSR DMF [Seq. No.]	Date Approved	Document(s) Affected	Overview of Changes
Pending [Minor Mod]	04/14/2017 [0009]	pending	Pharmacy Enrollment Form	Add field for name of back-up pharmacist-in-charge

2.8 Reviewer Guide

A reviewer guide should be included for all submissions that propose changes to the REMS, including revisions, minor modifications, major modifications, and modifications due to safety labeling changes. The reviewer guide should contain hyperlinks to the Word file for each (changed and unchanged) document. For documents that are being changed, link to the tracked version. For documents that are unchanged, link to the latest version of the document.

Example Reviewer Guide:

Document	Are changes proposed in this submission?	Date of latest Modification/Revision [17] [Type of REMS]	Total No. of Modifications/Revisions, to date
REMS document	N	03/15/2012 [Rev]	3
Prescriber letter	Y	09/04/2010 [Orig]	1
FAQs	N	04/21/2011 [Modi]	2
[…]	[…]	[…]	[…]

3 General Instructions for *Cross-Reference Submissions* to Individual New Drug Applications/Abbreviated New Drug Applications

As stated previously, for the purposes of this Guide, a *cross-reference submission* is the submission that an SSR applicant will make to their individual application, to incorporate by reference information that the holder has submitted to the SSR DMF.[18]

This section provides general information about cross-reference submissions.

Either before or at the time of their first cross-reference submission, SSR applicants should submit a copy of the holder's letter of authorization (LOA) to their respective applications (include in eCTD section 1.4.2 Statement of Right of Reference). This LOA

[17] The "date of latest modification/revision" for a document will be the "date approved" for a document that was changed as part of a REMS Modification supplement or the "date submitted" for a document that was changed as part of a REMS Revision.

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

only needs to be submitted once, unless there are changes to the holder name or the authorized party name.

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

A cross-reference submission <u>will</u> be needed after any of the following have been submitted to the SSR DMF:

- REMS Original
- Minor REMS Modification
- Major REMS Modification
- REMS Modifications Due to Safety Labeling Changes
- REMS Revision
- REMS Assessment[19]

The cross-reference submission for a REMS Original,[20] minor REMS modification, major REMS modification, and REMS modifications due to safety labeling changes should be submitted to the individual application as an amendment, if applicable, or a supplement. Submissions of REMS revisions[21] and REMS assessments are not supplemental applications; cross-reference submissions are still needed but should not be submitted as supplements.

A cross-reference submission <u>will not</u> be needed after the following have been submitted to the SSR DMF:

- REMS Assessment Methodology
- REMS Correspondence
- Interim versions of REMS documents, materials, or REMS supporting documents
- Responses to FDA's Information Requests
- Historical REMS submissions (See section 1, *General Instructions*)

[19] 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.

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

[21] See guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*, available at .http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm441226.pdf.

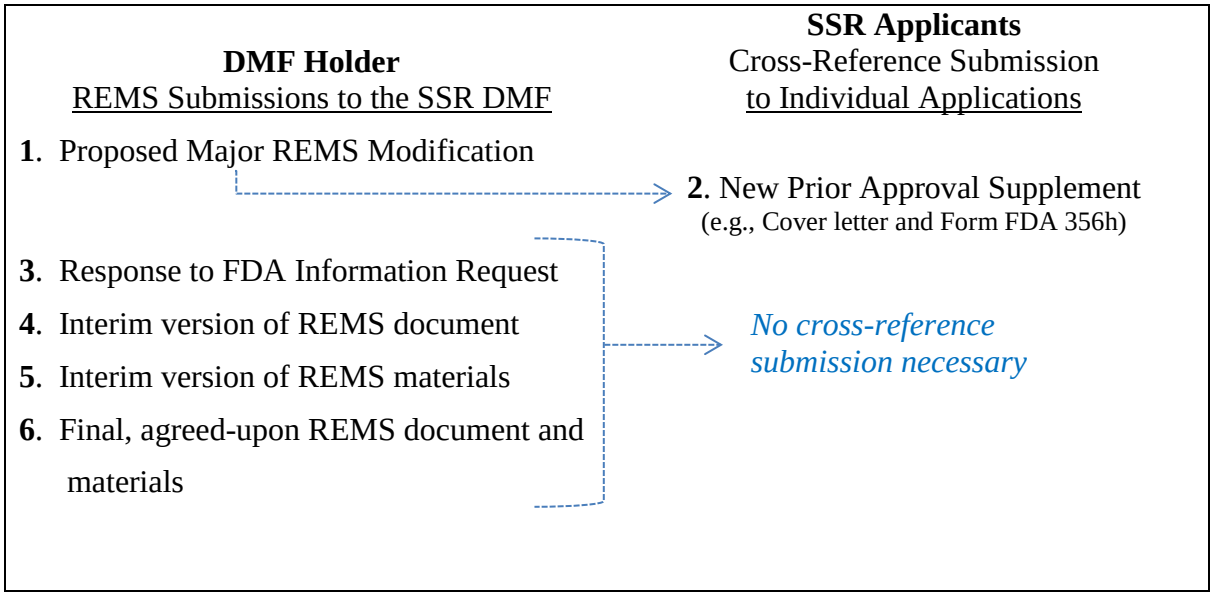
In most cases, the cross-reference submission will only include Form FDA 356h, a cover letter, and, as applicable, a Medication Guide.[22]

- The SSR DMF number should be listed in Field 30 "Cross References," of Form FDA 356h.

- The cover letter should cross-reference the REMS submission to the DMF, noting the DMF submission date and eCTD sequence number. It should also include any standard cover letter content or required submission identifiers. A cross-reference cover letter template is included in Appendix E.

Figure 1 provides an overview of the process for cross-reference submissions. The left column shows example submissions to the SSR DMF for a Major REMS modification, and the right column shows the corresponding cross-reference submission that should be submitted to each applicant's NDA/ANDA.

Figure 1: Cross-reference Submissions for a Major REMS Modification



[22] Medication Guides that are part of a REMS should be included in each applicant's cross-reference submission to their new drug application (NDA), biologics license application (BLA), or abbreviated new drug application (ANDA). 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.

4 Appendices

Appendix A: Detailed SSR DMF Submission Instructions

Appendix B: SSR DMF Cover Letter Template

Appendix C: SSR DMF Leaf Title and File Name Examples

Appendix D: REMS History and Reviewer Guide Examples

Appendix E: NDA/ANDA Cross-Reference Submission Letter Template

Appendix A: Detailed SSR DMF Submission Instructions

REMS Original SSR DMF Submission Instructions	
General	REMS Original supplements will include at least two submissions to the DMF: • A submission of the proposed or *draft* materials • A submission of the final, agreed-upon or *final* materials (i.e., the "Gold Standard Submission") Include all files listed below.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information 4. Reviewer Guide 5. REMS content (e.g., REMS document, REMS materials, and REMS supporting document)
1. Cover Letter	
Submission Category[23]	REMS Proposal/Standard Timeframe REMS/Final
Submission Description, examples	• Proposed REMS Program • Amendment [No.] to REMS Program Proposal, originally submitted to the SSR DMF on MM/DD/YYYY; Seq. 0001
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [Submission type = Original] **[Draft or Final]** [*If amending the original supplement/submission*, add "_Amendment" and the amendment # (as applicable)] **Examples:** **Cover letter** 0001 **20160314** Original_**Draft** C**over letter** 0002 **20160517** Original_**Draft**_Amendment 1 C**over letter** 0003 **20160912** Original_**Final**
Suggested File Name	cover-letter-rems original-YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
4. Reviewer Guide	
File Format	PDF
eCTD Module 1 Heading	1.2
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Reviewer Guide REMS Original
Suggested File Name	reviewer-guide-rems-original-YYYYMMDD
Template and/or Examples	See **Appendix D**

[23] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

REMS Original (cont.) SSR DMF Submission Instructions	
5. REMS Content **Note:** Because of the numerous files that are included in REMS original submissions (e.g., REMS document, REMS materials, REMS supporting document), a list of suggested leaf titles and file names is included in Appendix C.	
File Format	Word and PDF (See *Document Organization* below)
eCTD Module 1 Heading	1.16
Leaf Subheading[24]	Draft Final
Leaf Title	See **Appendix C** for examples Leaf titles should be short, meaningful, and indicative of each document's content.
Suggested File Name	**Format:** [*stakeholder*]-**[form or document type]** **Examples**: *prescriber*-**letter** *pharmacy*-**enrollment-form** A stakeholder does not need to be specified for documents that apply to multiple stakeholders (e.g., REMS Program Web site = web site). If a document contains **tracked changes** or **annotations**, this should be reflected in the file name and leaf title. For example: prescriber letter-tracked. See **Appendix C** for additional examples
Template and/or Examples	N/A
Document Organization:	Submissions will generally include a combination of "aggregate files" and "individual files." The following files should be included for REMS Original submissions: • **One aggregate PDF file** that includes the **REMS document + all appended REMS materials**[25] The order of the documents in this file should correspond with the order in which they are listed in the REMS document, unless otherwise specified by FDA. Top-level bookmarks should be created for each individual document (the bookmark name should reference/include the document name). Additional bookmarks may be created under the top-level bookmarks, as needed. All other bookmarks created, such as headings within the REMS document that are automatically bookmarked, should be removed. • **One individual PDF file** of the **REMS supporting document** • **An individual Word file**[26] **for each document in the REMS**, i.e., a Word file for the REMS document, the REMS supporting document, and for each appended REMS material. Note: See PDF Specifications on the FDA eCTD web site. (www.fda.gov/ectd) for additional guidance on organization of PDF files.

[24] If you are using the eCTD Backbone Files Specification for Module 1 Version 2.3 (DTD v3.3), you do not need to create leaf title subheadings since REMS 1.16 includes subheadings. For placement of documents see https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm535180.htm.

[25] Appended REMS materials = all documents that are listed in the REMS as "part of the REMS and is/are appended."

[26] The individual Word files do not need to be submitted as individual PDF files; the PDF files described in "Document Organization" above will serve as the archival copies. However, FDA recognizes that some materials, such as web site screenshots, are not available in Word, and therefore, can be submitted as an individual PDF file.

REMS Revision SSR DMF Submission Instructions	
General	REMS Revisions may include only one submission to the DMF. Include all files listed below in the xml eCTD backbone.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information 4. Reviewer Guide 5. REMS History 6. REMS content (e.g. REMS document, REMS materials, and REMS supporting document, as appropriate)
1. Cover Letter	
Submission Category[27]	REMS Revisions
Submission Description, example	REMS Revision to [brief description of change]
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [Submission type = Revision] **Example(s):** **Cover letter** 0004 **20160614** Revision **Cover letter** 0005 **20160701** Revision
Suggested File Name	cover-letter-revision-YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
4. Reviewer Guide	
File Format	PDF
eCTD Module 1 Heading	1.2
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Reviewer Guide Revision
Suggested File Name	reviewer-guide-revision-YYYYMMDD
Template and/or Examples	See **Appendix D**
5. REMS History	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	REMS History YYYYMMDD
Suggested File Name	rems-history-YYYYMMDD
Template and/or Examples	See **Appendix D**

[27] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

REMS Revision (cont.) SSR DMF Submission Instructions	
6. REMS Content **Note:** Because of the numerous REMS files that may be included in REMS revision submissions (e.g., REMS document, REMS materials, REMS supporting document), the list of suggested leaf titles and file names is included in Appendix C.	
File Format	Word and PDF (See *Document Organization* below)
eCTD Module 1 Heading	1.16
Leaf Subheading	Final Draft (for the tracked documents)
Leaf Title	See **Appendix C** for examples Leaf titles should be short, meaningful, and indicative of each document's content.
Suggested File Name	**Format:** [*stakeholder*] **[form or document type]** **Examples**: *prescriber*-**letter** *pharmacy*-**enrollment-form** A stakeholder does not need to be specified for documents that apply to multiple stakeholders (e.g., REMS Program Web site = web site) If a document contains **track changes** or **annotations**, this should be reflected in the file name and leaf title. For example: prescriber letter-tracked. See **Appendix C** for additional examples.
Template and/or Examples	N/A
Document Organization:	Submissions will include a combination of "aggregate files" and "individual files." The following files should be included for all REMS Revision submissions: • **One PDF file** that includes clean versions of the **REMS document + all appended REMS materials** The order of the documents in this file should correspond with the order in which they are listed in the REMS document, unless otherwise specified by FDA. Top-level bookmarks should be created for each individual document (the bookmark name should reference/include the document name). Additional bookmarks may be created under the top-level bookmarks, as needed. All other bookmarks created, such as headings within the REMS document that are automatically bookmarked, should be removed. • **One PDF file** that includes the clean **REMS supporting document** • **Individual Word files**[28] for each document that is being changed, include an individual clean and an individual tracked version of the document, i.e., if only the REMS document was changed, submit a clean and a tracked Word file for the REMS document. Individual Word files for the documents that are not being changed do not need to be submitted; reviewers will access "unchanged" documents via the hyperlinked Reviewer Guide or via the eCTD viewer software. Note: See PDF Specifications on the FDA eCTD web site (www.fda.gov/ectd) for additional guidance on organization of PDF files.

[28] The individual Word files do not need to be submitted as individual PDF files; the PDF files described in "Document Organization" above will serve as the archival copies. However, FDA recognizes that some materials, such as web site screenshots, are not available in Word, and therefore, can be submitted as an individual PDF file.

REMS Minor Modification SSR DMF Submission Instructions	
General	REMS Minor Modifications should include at least two submissions to the DMF: • A submission of the proposed *Draft* materials • A submission of the final, agreed-upon, of *Final* materials (i.e., the "Gold Standard Submission") Include all files listed below in the xml eCTD backbone.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information 4. Reviewer Guide 5. REMS History 6. REMS content (e.g., REMS document, REMS materials, and REMS supporting document, as appropriate)
1. Cover Letter	
Submission Category[29]	REMS Modification/Minor Modifications
Submission Description, examples	• Proposed Minor REMS Modification to [brief description of change] • Amendment [No.] to Minor REMS Modification, originally submitted to the SSR DMF on MM/DD/YYYY; Seq. 0001
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [Submission type = Minor Modification] **[Draft or Final]** [*If amending the original supplement/submission, add* "_Amendment" *and the amendment # (as applicable)*] **Example(s):** **Cover letter** 0004 **20160614** Minor Mod**_Draft** **Cover letter** 0005 **20160701** Minor Mod **_Draft** _Amendment 1 **Cover letter** 0006 **20160824** Minor Mod **_Draft** _Amendment 2 **Cover letter** 0008 **20161003** Minor Mod **_Final**
Suggested File Name	cover-letter-minor-mod-YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
4. Reviewer Guide	
File Format	PDF
eCTD Module 1 Heading	1.2
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Reviewer Guide Minor Modification
Suggested File Name	reviewer-guide-minor-mod YYYYMMDD
Template and/or Examples	See **Appendix D**

[29] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

REMS Minor Modification (cont.) SSR DMF Submission Instructions	
5. REMS History	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	REMS History YYYYMMDD
Suggested File Name	REMS-history-YYYYMMDD
Template and/or Examples	See **Appendix D**
6. REMS Content **Note:** Because of the numerous REMS files that may be included in REMS minor modification submissions (e.g., REMS document, REMS materials, REMS supporting document), the list of suggested leaf titles and file names is included in Appendix C.	
File Format	Word and PDF (See *Document Organization* below)
eCTD Module 1 Heading	1.16
Leaf Subheading	Draft or Final
Leaf Title	See **Appendix C** for examples Leaf titles should be short, meaningful, and indicative of each document's content.
Suggested File Name	**Format:** [*stakeholder*] **[form or document type]** **Examples**: *prescriber*-**letter** *pharmacy*-**enrollment-form** A stakeholder does not need to be specified for documents that apply to multiple stakeholders (e.g., REMS Program Web site = web site) If a document contains **track changes** or **annotations**, this should be reflected in the file name and leaf title. For example: prescriber letter-tracked. See **Appendix C** for additional examples
Template and/or Examples	N/A
Document Organization:	Submissions will generally include a combination of "aggregate files" and "individual files." The following files should be included for all REMS Minor Modification submissions: • **One PDF file** that includes the **REMS document + all appended REMS materials** The order of the documents in this file should correspond with the order in which they are listed in the REMS document, unless otherwise specified by FDA. Top-level bookmarks should be created for each individual document (the bookmark name should reference/include the document name). Additional bookmarks may be created under the top-level bookmarks, as needed. All other bookmarks created, such as headings within the REMS document that are automatically bookmarked, should be removed. *For submissions that contain Draft materials*: This PDF file should contain all changed and unchanged documents. Include the tracked version of documents that are being changed. • **One PDF file** that includes the **REMS supporting document** *For submissions that contain Draft materials*: If the REMS supporting document is one of the documents being changed, this PDF should be the tracked version of the document. • **An individual Word file[30] for each document in the REMS**, i.e., a Word file for the REMS document, the REMS supporting document, and for each appended REMS material. *For all REMS submissions (Draft or Final)* an individual Word file should be

[30] The individual Word files do not need to be submitted as individual PDF files; the PDF files described in "Document Organization" above will serve as the archival copies. However, FDA recognizes that some materials, such as web site screenshots, are not available in Word, and therefore, can be submitted as an individual PDF file.

	submitted only for those documents that are being changed (for *Draft* submissions, these Word files should be tracked and annotated). Individual Word files for the documents that are not being changed do not need to be submitted; reviewers will access "unchanged" documents via the hyperlinked Reviewer Guide or via the eCTD viewer software. Note: See PDF Specifications on the FDA eCTD web site (https://www.fda.gov/ectd) for additional guidance on the organization of PDF files.

REMS Major Modification SSR DMF Submission Instructions	
General	REMS Major Modifications should include at least two submissions to the DMF: • A submission of the proposed *Draft* materials • A submission of the final, agreed-upon, of *Final* materials (i.e., the "Gold Standard Submission"). Include all files listed below in the xml eCTD backbone.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information 4. Reviewer Guide 5. REMS History 6. REMS content (e.g., REMS document, REMS materials, and REMS supporting document, as appropriate)
1. Cover Letter	
Submission Category[31]	REMS Modification/Major Modifications
Submission Description, examples	• Proposed Major REMS Modification to [brief description of change] • Amendment [No.] to Major REMS Modification, originally submitted to the SSR DMF on MM/DD/YYYY; Seq. 0001
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [Submission type = Major Modification] **[Draft or Final]** [*If amending the original supplement/submission*, add "_Amendment" and the amendment **No.** (as applicable)] **Example(s):** **Cover letter** 0004 **20160614** Major Mod**_Draft** **Cover letter** 0005 **20160701** Major Mod**_Draft**_Amendment 1 **Cover letter** 0006 **20160824** Major Mod**_Draft**_Amendment 2 **Cover letter** 0008 **20161003** Major Mod**_Final**
Suggested File Name	cover-letter-major-mod-YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
4. Reviewer Guide	
File Format	PDF
eCTD Module 1 Heading	1.2
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Reviewer Guide Major Modification
Suggested File Name	reviewer-guide-major-mod-YYYYMMDD
Template and/or Examples	See **Appendix D**

[31] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

REMS Major Modification (cont.) SSR DMF Submission Instructions	
5. REMS History	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	REMS History YYYYMMDD
Suggested File Name	rems-history-YYYYMMDD
Template and/or Examples	See **Appendix D**
6. REMS Content Note: Because of the numerous REMS files that may be included in REMS major modification submissions (e.g., REMS document, REMS materials appended to the REMS, REMS supporting document), the list of suggested leaf titles and file names is included in Appendix C.	
File Format	Word and PDF (See *Document Organization* below)
eCTD Module 1 Heading	1.16
Leaf Subheading	Draft or Final
Leaf Title	See **Appendix C** for examples Leaf titles should be short, meaningful, and indicative of each document's content.
Suggested File Name	**Format:** [*stakeholder*] **[form or document type]** **Examples**: *prescriber*-**letter** *pharmacy*-**enrollment-form** A stakeholder does not need to be specified for documents that apply to multiple stakeholders (e.g., REMS Program Web site = web site) If a document contains **track changes** or **annotations**, this should be reflected in the file name and leaf title. For example: prescriber letter-tracked. See **Appendix C** for additional examples
Template and/or Examples	N/A
Document Organization:	Submissions will generally include a combination of "aggregate files" and "individual files." The following files should be included for all REMS Major Modification submissions: • **One PDF file** that includes the **REMS document + all appended REMS materials** The order of the documents in this file should correspond with the order in which they are listed in the REMS document, unless otherwise specified by FDA. Top-level bookmarks should be created for each individual document (the bookmark name should reference/include the document name). Additional bookmarks may be created under the top-level bookmarks, as needed. All other bookmarks created, such as headings within the REMS document that are automatically bookmarked, should be removed. <u>*For submissions that contain Draft materials*</u>: This PDF file should contain all changed and unchanged documents. Include the tracked version of documents that are being changed. • **One PDF file** that includes the **REMS supporting document** <u>*For submissions that contain Draft materials*</u>: If the REMS supporting document is one of the documents being changed, this PDF should be the tracked version of the document. • **An individual Word file[32] for each document in the REMS**, i.e., a Word file for the REMS document, the REMS supporting document, and for each appended REMS material.

[32] The individual Word files do not need to be submitted as individual PDF files; the PDF files described in "Document Organization" above will serve as the archival copies. However, FDA recognizes that some materials, such as Web site screenshots, are not available in Word, and therefore, can be submitted as an individual PDF file.

	For all REMS submissions (Draft or Final): An individual Word file should be submitted only for those documents that are being changed (for *Draft* submissions, these Word files should be tracked and annotated). Individual Word files for the documents that are not being changed do not need to be submitted; reviewers will access "unchanged" documents via the hyperlinked Reviewer Guide or via the eCTD viewer software. Note: See PDF Specifications on the FDA eCTD web site (www.fda.gov/ectd) for additional guidance on the organization of PDF files.

REMS Modification Due to Safety Labeling Changes SSR DMF Submission Instructions	
General	REMS Modifications Due to Safety Labeling Changes are considered Major Modifications. Please contact the FDA Project Manager assigned as the point-of-contact for your SSR, as soon as possible, for information on how to submit to the DMF, and how applicants should submit to their individual applications.

REMS Assessment SSR DMF Submission Instructions	
General	Use the operation attribute "**New**" for each new assessment. Include all files listed below in the xml eCTD backbone.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information 4. REMS History 5. REMS Assessment
1. Cover Letter	
Submission Category [33]	REMS Assessment
Submission Description, examples	• Assessment [No.] at [timetable reference] • Amendment [No.] to Assessment [No.] at [timetable reference], originally submitted to the SSR DMF on MM/DD/YYYY; Seq. 0001
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [Assessment] [Assessment No.] **[Timetable reference]** [*If relevant*, add "_Amendment" *] **Examples:** **Cover letter** 0003 **20130914** Assessment 1 **at 6 months** **Cover letter** 0004 **20130928** Assessment 1 **at 6 months**_Amendment **Cover letter** 0008 **20130314** Assessment 2 **at 1 year** * For example, if the agency requests additional information or clarification of your assessment results, your response to that request would be submitted as an "Amendment" to the original Assessment submission.
Suggested File Name	cover-letter-assessment [Assessment No.]YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
3. REMS History	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	REMS History YYYYMMDD
Suggested File Name	rems-history-YYYYMMDD
Template and/or Examples	See **Appendix D**

[33] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

REMS Assessment (cont.) SSR DMF Submission Instructions	
4. REMS Assessment Content	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	**Format:** *Assessment [Assessment No.]* **[Timetable reference]** **Examples:** *Assessment 2* **12 month** *Assessment 3* **2 year**
Suggested File Names	assessment-[assessment no.]-[timetable reference]

REMS Assessment Methodology SSR DMF Submission Instructions	
General	Include all files listed below in the xml eCTD backbone.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information 4. REMS Assessment Methodology
1. Cover Letter	
Submission Category[34]	REMS Assessment Methodology
Submission Description, examples	REMS Assessment Methodology [add short descriptor, e.g. Survey]
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [Methodology] [- Survey *or* - Other] **Example:** **Cover letter** 0007 **20131015** Methodology – Survey
Suggested File Name	cover-letter-methodology-[add short descriptor]YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
4. REMS Assessment Methodology	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	Methodology Survey [add short descriptor] Methodology Other [add short descriptor]
Suggested File Names	Methodology-survey-[add short descriptor] Methodology-other-[add short descriptor]

[34] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

REMS Correspondence SSR DMF Submission Instructions	
General	General correspondence about an approved REMS that does not fit into one of the categories described previously (and that does not relate to a specific supplement or assessment that is under review) should be submitted as REMS correspondence.
Documents to Include in this Submission	1. Cover Letter 2. Statement of Commitment 3. Administrative Information Page 4. REMS Correspondence
1. Cover Letter	
Submission Category[35]	REMS Correspondence
Submission Description, examples	Include a concise description of the contents
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	**Format:** **Cover letter** [Sequence No.] **[Date YYYYMMDD]** [REMS Correspondence] **Example:** **Cover letter** 0010 **20131015** REMS Correspondence
Suggested File Name	cover-letter-correspondence [add short descriptor]YYYYMMDD
Template and/or Examples	See **Appendix B**
2. Statement of Commitment	
File Format	PDF
eCTD Module 1 Heading	1.2 Cover Letters
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Statement of Commitment
Suggested File Name	statement-of-commitment-YYYYMMDD
3. Administrative Information	
File Format	PDF
eCTD Module 1 Heading	1.3 Administrative Information
Leaf Subheading	N/A
Leaf Title	[Sequence No.] [**YYYYMMDD**] Administrative Information
Suggested File Name	admin-info-YYYYMMDD
4. REMS Correspondence	
File Format	PDF
eCTD Module 1 Heading	1.16
Leaf Subheading	N/A
Leaf Title	Correspondence [add short descriptor]
Suggested File Names	Will depend on what is being submitted

[35] Enter this information in the corresponding section of the cover letter; see cover letter template in Appendix B.

Appendix B: SSR DMF Cover Letter Template

Cover Letter Template: SSR DMF Submissions

- Notes and examples are in *italics*
- Information to be filled in is in [brackets]

Date: [Current Date on day of submission]

DMF#: [DMF number]

Holder: [Name of Holder]

Subject (Title): [Subject of the DMF as it appears on the DMF Web site[36]]

Re: REMS Shared System Program

DMF Type: V

Submission Category(ies)/Subcategory(ies): [Submission Category(ies)/Subcategory(ies)]
There are different submission categories for different types of submission content. Identify the appropriate DMF-related and/or REMS-related submission category(ies). If the submission contains more than one type of submission content, all submission categories should be included.

Categories/Subcategories for DMF-related content:

New/Master File

DMF Amendment/Annual Report

Letter of Authorization/Letter of Authorization

Letter of Authorization/Withdrawn Letter of Authorization

Categories/Subcategories for REMS-related content:

REMS Proposal/Standard Timeframe

REMS/Final

REMS Revision

REMS Modification/Major Modifications

REMS Modification/Minor Modifications

REMS Modification/Due to Safety Labeling Changes[37]

REMS Modification/REMS Assessment

REMS Assessment

REMS Assessment Methodology

REMS Correspondence

Submission Description: [Include a brief description of the purpose of the submission and/or contents; refer to the relevant submission type in Appendix A for example submission descriptions.]

eCTD Sequence Number: [XXXX]

[Body of the letter]

Sincerely,

Signature of Responsible Official
[Name of Responsible Official
Responsible Official's Title
Responsible Official's Company, i.e., Holder or Agent
Responsible Official's Telephone number
Responsible Official's Fax number
Responsible Official's Email address]

---

[36] The "subject of the DMF as it appears on the DMF Web site" should be the same for every submission to this DMF: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm.

[37] Please contact the FDA Project Manager assigned as the point-of-contact for your SSR for instructions on submitting REMS Modifications Due to Safety Labeling Changes.

Appendix C: SSR DMF Leaf Title and File Name Examples

General:

- **The format for leaf titles is:** [Leaf title sub-heading] [Leaf title].
  Examples: "Draft Supporting Document" "Final Supporting Document"
- Include all files listed below in the xml eCTD backbone, in section 1.16 of the DMF.
- For Individual Files, if a document includes track changes and/or annotations, this should be reflected in the file name.
  Examples: "draft rems-tracked," "draft rems-clean"

Submission Types: REMS Original REMS Modifications (all types) REMS Revisions		
Leaf Title Subheading & Leaf Title	**Suggested File names**	**NOTES**
PDF Files		
Draft REMS and Materials Final REMS and Materials	rems-and-materials	This PDF includes the REMS document and all appended REMS materials.
Draft Supporting Document Final Supporting Document	supporting-document	
Individual Files (Word in most cases)		
Draft REMS Final REMS	rems-document	REMS document only
Draft Supporting Document Final Supporting Document	supporting-document	
Draft Prescriber Overview Final Prescriber Overview	prescriber-overview	
Draft Education Program Final Education Program	education-program	
Draft Prescriber Enrollment Form Final Prescriber Enrollment Form	prescriber-enrollment-form	
Draft Patient Counseling Doc Final Patient Counseling Doc	patient-counseling-doc	
Draft FAQ Final FAQ	Faq	
Draft Web site Final Web site	web site	
Draft Prescriber Letter Final Prescriber Letter	prescriber-letter	
Draft Professional Org Letter Final Professional Org Letter	prof-org-letter	
Draft Pharm Overview Final Pharm Overview	pharm-overview	
Draft Distributor Letter Final Distributor Letter	distributor-letter	

Appendix D: REMS History and Reviewer Guide Examples

(Note: Sections 2.7 and 2.8 of this document are repeated here in Appendix D, for ease of reference.)

REMS History

The REMS history provides a summary of all changes to the REMS since approval and all REMS assessments to date. It should be submitted with REMS assessments and with each submission that proposes changes to the REMS (revisions, minor modifications, major modifications, and modifications due to safety labeling changes). The REMS history can be included in the cover letter or submitted as a single PDF file. The instructions for submitting the REMS history as a single PDF file are included in Appendix A.

The REMS history should be similar in format to the summary that application holders include in labeling supplements that provides the history of changes made to the product labeling. The REMS history should be in tabular format and should contain the REMS assessment number or the type of REMS change. The REMS history should also contain a brief overview of the revisions or modifications, list the REMS materials affected, and, in the case of REMS modifications, provide either the date of submission (for REMS revisions and pending modifications) or approval.

Example of a REMS History:

Assessment No. or [Type of REMS change]	Date Submitted to SSR DMF [Seq. No.]	Date Approved	Document(s) Affected	Overview of Changes
Original	01/01/2015 [0001]	10/02/2015	Original REMS	N/A
[Major Mod]	02/22/2016 [0003]	08/08/2016	• REMS Document • Prescriber Enrollment Form • FAQ • Supporting Document	Changed to address the addition of permanent AF to the Contraindications Section of the Prescribing Information
Assessment 1 @ 6 months	04/02/2016 [0005]	N/A	N/A	N/A
[Revision]	12/06/2016 [0007]	N/A	Prescriber Brochure	Fixed punctuation
Pending [Minor Mod]	04/14/2017 [0009]	pending	Pharmacy Enrollment Form	Add field for name of back-up pharmacist-in-charge

Reviewer Guide

A reviewer guide should be included for all submissions that propose changes to the REMS, including revisions, minor modifications, major modifications, and modifications due to safety labeling changes. The reviewer guide should contain hyperlinks to the Word file for each (changed and unchanged) document. For documents that are being changed, link to the tracked version. For documents that are unchanged, link to the latest version of the document.

Example Reviewer Guide:

Document	Are changes proposed in this submission?	Date of latest Modification/Revision[38] [Type of REMS Change]	Total number of Modifications/Revisions, to date
rems document	N	03/15/2012 [Rev]	3
prescriber letter	Y	09/04/2010 [Orig]	1
FAQ	N	04/21/2011 [Mod]	2
[…]	[…]	[…]	[…]

[38] The "date of latest modification/revision" for a document will be the "date approved" for a document that was changed as part of a REMS Modification supplement or the "date submitted" for a document that was changed as part of a REMS Revision.

Appendix E: NDA/ANDA Cross-Reference Submission Cover Letter Template

Cover Letter Template: NDA/ANDA Cross-Reference Submission

- Notes and examples are in *italics*
- Information to be filled in is in [brackets]
  Note: The options that are presented within the brackets (e.g., the options for Submission Type) are limited to those that are relevant to cross-reference submissions.

The cover letter "to cross-reference a REMS submission to the SSR DMF" will essentially be the same as the corresponding cover letters for a "REMS submission to an individual application," and should include any standard cover letter content and required submission categories/subcategories. The example template below is intended to illustrate the types of information to capture in a cross-reference cover letter. Applicants are not expected to adopt this format and/or modify their standard approach to cover letters.

[Date]

[Inside Address]

Product Name: [Proprietary Name (established name)]

[NDA# or ANDA#]: [Assigned #]

eCTD Seq. No.: [Sequence Number]

Submission Sub-Type: (*if applicable)* [New Supplement, Amendment] [Supplement Number *(if applicable)*]

Submission Type: [PAS, CBE-30, REMS Revision, REMS Assessment]

Subject: [Enter the appropriate REMS submission category(ies)/subcategory(ies)]

REMS Proposal/Standard Timeframe
REMS/Final
REMS Assessment
REMS Revision
REMS Modification/Major Modifications
REMS Modification/Minor Modifications
REMS Modification/Due to Safety Labeling Changes[39]
REMS Modification/REMS Assessment

[Salutation]

[Body of the letter]

The cover letter should include a cross-reference to the REMS submission to the DMF, along with the date the submission was made to the DMF, and the DMF eCTD sequence number.

Sincerely,

Signature of Responsible Official
[Name of Responsible Official
Responsible Official's Title
Responsible Official's Company
Responsible Official's Telephone number
Responsible Official's Fax number\
Responsible Official's Email address]

[39] Please contact the FDA Project Manager assigned as the point-of-contact for your SSR for instructions on submitting REMS Modifications Due to Safety Label Changes.