
Format and Content of a REMS Document Guidance for Industry

**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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This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) document for a prescription drug product, including a biological drug product.² A REMS document, which is part of a REMS that is required by FDA, establishes the goals and requirements of the REMS.

This guidance provides recommendations to applicants on drafting proposed REMS documents and converting an already-approved REMS document to a new, standardized format that is clearer, more informative, and supports submission of a REMS document in Structured Product Labeling (SPL) format.

This guidance provides an overview of the types of information that should be included in a REMS document. Additional and more detailed information is provided in a separate guide, *REMS Document Technical Conformance Guide*, which will be updated periodically and is available on FDA's website.³ The guide can be used for drafting a REMS document for single product and shared system REMS and includes an outline for drafting a Bifurcated⁴ REMS document. This guidance and the technical conformance guide are intended to help ensure that

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

² For purposes of this guidance, unless otherwise specified, references to *drugs* and *drug products* include drugs submitted for approval or approved under sections 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 (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)). These applications are termed *covered applications* and refer to new drug applications (NDAs), abbreviated new drug applications (ANDAs) and biologics license applications (BLAs).

³ See the *REMS Document Technical Conformance Guide* that includes the *REMS Document Template* and the *Bifurcated REMS Document Outline*. For the most recent version of this technical conformance guide, go to <https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/roles-different-participants-rems>.

⁴ A Bifurcated REMS Document is used when the approval of a shared system REMS may coincide with tentative approval of an ANDA or section 505(b)(2) application. For more information, refer to the guidance for industry, *Development of a Shared System or Separate Comparable REMS* (June, 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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REMS documents are clear, understandable to stakeholders, and to the extent possible, consistent in content and format, and support submission of a REMS document in SPL format.

This guidance does not provide detailed information on the format and content of other documents that are part of a REMS submission, such as the REMS materials⁵ or the REMS supporting document.⁶ Furthermore, the guidance does not include information on how to design, implement, and evaluate a REMS or to submit revisions and modifications for a REMS.

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. FDA's REMS Authority

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 355-1) establishes FDA's REMS authority. A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks.

If FDA determines that a REMS is necessary,⁷ the Agency may require one or more REMS elements, which could include a Medication Guide, a patient package insert, a communication plan and/or certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose.⁸ FDA may also require elements to assure safe use (ETASU) as part of a REMS.⁹ ETASU may be required if the drug has been shown to be effective, but is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate a specific serious risk(s) listed in the labeling of the drug. ETASU may be required for drug products initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.

Specifically, ETASU may include one or any combination of the following requirements:¹⁰

⁵ All proposed materials that are included as part of the REMS (e.g., communication and educational materials, enrollment forms, prescriber and patient agreements) are also approved and are appended to the REMS document. This guidance refers to these materials as *REMS materials*.

⁶ For purposes of this guidance, the *REMS supporting document* expands on information in the REMS document and provides additional information about the REMS, such as the rationale for, and supporting information about, the design, implementation, and assessment of the REMS.

⁷ See guidance for industry *FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019).

⁸ Section 505-1(e)(2)-(4) of the FD&C Act.

⁹ See section 505-1(f) of the FD&C Act.

¹⁰ See section 505-1(f)(3) of the FD&C Act.

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- Health care providers who prescribe the drug have particular training or experience, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug be dispensed to patients only in certain health care settings, such as hospitals
- The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
- Each patient using the drug be subject to monitoring
- Each patient using the drug be enrolled in a registry

If a REMS includes certain ETASU, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the element(s) (e.g., development of a REMS specific website or call center to facilitate enrollment; establishment of electronic databases of certified health care settings).¹¹

All REMS should include one or more goals. If the REMS has ETASU, the REMS must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug and for which the ETASU are required.¹²

Finally, REMS generally must include a timetable for submission of assessments of the REMS.¹³ The timetable for submission of assessments of the REMS must include an assessment by the dates that are 18 months and 3 years after the REMS is initially approved, and an assessment in the 7th year after the REMS is approved, or at another frequency specified in the REMS.¹⁴

B. FDA's Considerations for Changing the Format of the REMS Document

Since the approval of the first REMS in 2008, FDA has received public feedback on improving the REMS document.^{15,16} FDA has revised its recommendations on the format and content of the REMS document in response to the public's feedback and to provide assistance with drafting a clearer, more informative, and standardized document. Additionally, this format supports submission of REMS documents in SPL format.^{17,18}

¹¹ See section 505-1(f)(4) of the FD&C Act.

¹² See section 505-1(f)(3) of the FD&C Act.

¹³ NDAs and BLAs must include a timetable for submission of assessments. ANDAs are not subject to the requirement for a timetable for submission of assessments (section 505-1(i)), but FDA can require any application holder, including ANDA applicants, to submit REMS assessments under section 505-1(g)(2)(C).

¹⁴ See section 505-1(d) of the FD&C Act; see also section 505-1(g)(2) of the FD&C Act.

¹⁵ See <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

¹⁶ See <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm350852.htm>.

¹⁷ Structured product labeling (SPL) is a document markup standard approved by Health Level Seven and adopted by FDA as a mechanism for exchanging product and facility information.

¹⁸ See additional information on REMS SPL, available at <https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm517343.htm>.

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The current format for the REMS document organizes the REMS requirements by who is responsible for implementing the requirement, when the requirement is to be implemented, what action is required, and with what REMS material(s). This format also makes greater use of tables and bulleted lists to better present and organize the information.

III. FORMAT AND CONTENT OF A REMS DOCUMENT

A REMS document establishes the goals and requirements²⁰ of the REMS as they relate to the required REMS elements. This information is described in more detail in the sections below.

To facilitate the applicant's implementation of the recommended format, FDA has developed a technical conformance guide to use in conjunction with this guidance. The *REMS Document Technical Conformance Guide* is available on FDA's website, at <https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/roles-different-participants-rems>

As described here, the technical conformance guide contains specific sections and provides standardized language to describe common REMS requirements. The standardized language was developed by FDA after review and comparison of existing approved REMS documents, consideration of stakeholder feedback on REMS documents, and FDA's experience in reviewing REMS and implementing its REMS authorities. It is the Agency's view that where REMS requirements are the same across REMS, the language used to describe the requirements should be consistent. FDA recommends that applicants use the standardized language whenever possible to help ensure consistency and facilitate efficient review of the REMS document. If alternative language is proposed, FDA recommends that applicants provide an explanation for their proposed language.

A. Administrative Information

The Administrative Information section should include relevant administrative information such as the application number(s), application holder's name, the date that the REMS was initially approved, the date of the most recent revision or modification of the REMS, and the risk(s) addressed by the REMS.

B. REMS Goals

The REMS Goals section should describe the overall, safety-related health outcome(s) that the REMS is designed to achieve. Because risk mitigation goals cannot always be measured directly, it is important to also include one or more specific, measurable objectives that, if achieved, indicate that the REMS is meeting its goals. For example, a REMS for a drug that causes renal toxicity may include a goal to mitigate the risk of renal failure, and the measurable objectives could be that patients undergo periodic monitoring of serum creatinine and that appropriate management steps are undertaken based on the test results.

C. REMS Requirements

The REMS Requirements section should establish the requirements of the REMS for both the REMS participant(s) and the applicant(s). REMS participants are stakeholders who participate

²⁰ Section 505-1 of the FD&C Act (21 U.S.C. 355-1).

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in the REMS based on their role in clinical assessment, prescribing, dispensing, administering, or monitoring, as well as the distribution process. They can include health care providers who prescribe, patients who receive the drug, health care settings, practitioners, pharmacies that dispense, and wholesalers-distributors that distribute.

The REMS Requirements section should be divided into the following subsections:

1. REMS Participant Requirements

The REMS Participant Requirements are the activities that REMS participants must undertake in REMS with ETASU.

If there are no requirements for REMS participants to carry out, the REMS Participant Requirements section should **not** be included in a REMS document.

In the REMS document, REMS Participant Requirements should be presented as a series of tables. There should be a separate table for each type of participant and each table should be formatted as follows:

1. [REMS Participant]	
[Timing Category]	<ol style="list-style-type: none">1. [REMS Requirement] using [REMS material]2. [REMS Requirement]
[Timing Category]	<ol style="list-style-type: none">3. [REMS Requirement]4. [REMS Requirement]

The table describes the participant *who* is responsible for complying with the requirement(s), *what* requirement(s) each participant needs to carry out, *when* the participant should perform each requirement(s), and *with what* REMS material(s). These items are described in further detail, below.

[REMS Participant]: REMS participants are stakeholders who participate in the REMS and are described based on their role in clinical assessment, prescribing, dispensing, administering, or monitoring as well as the distribution process. For example, REMS participants can include health care providers who prescribe; patients who receive the drug; health care settings, practitioners, and pharmacies that dispense; and wholesalers-distributors.

[Timing Category]: The timing category refers to *when* the participant must carry out the requirement (e.g., before a patient initiates treatment, during treatment, or after treatment discontinuation), and generally is associated with either a clinical activity (e.g.,

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initiating treatment or discontinuing treatment), or an administrative activity (e.g., becoming certified to prescribe²¹).

[Requirement]: Participant requirements generally include clinical or administrative activities that the participant must comply with as part of the REMS. An example of a clinical requirement is “Monitor the patient for injection site reactions.” An example of an administrative requirement is “Enroll the patient in the REMS.”²² In addition, some administrative requirements refer to “documentation of safe use conditions,”²³ which are activities that help ensure that health care providers or patients meet specified criteria before the drug is dispensed. For example, documentation of safe use conditions can include verifying that the prescriber is certified or that a required lab test was completed.

[REMS Material(s)]: Materials, such as enrollment forms and educational materials, refer to the specific documents that participants need to use to comply with a requirement. They should be included as a hyperlink in the REMS document within the requirement text that directs readers to the material.²⁴

2. REMS Applicant Requirements

The REMS Applicant Requirements are generally the requirements for applicants to: (1) develop and provide REMS training; (2) develop and provide packaging and disposal systems; (3) develop and disseminate REMS communications; (4) support REMS operations; and (5) ensure participants’ compliance with the REMS. A REMS may include some or all of these types of requirements.

Requirements related to training can include the requirement for the applicant to develop REMS training materials, to provide training to health care providers, and to develop a knowledge assessment for health care providers to complete as part of the training. The REMS training requirements should include information about how the training is being provided (e.g., website, mailing, in-person) and whether the training is being provided by a continuing education provider.

Requirements related to packaging and disposal can include requirements for the applicant to make a drug available for dispensing in certain packaging (e.g., unit dose) or implement a requirement that a disposal system be dispensed (for the purpose of rendering the drug nonretrievable). The packaging and disposal requirements can be

²¹ Certification requires that health care providers, pharmacies, or health care settings meet certain REMS requirements to be able to prescribe, dispense, or order a drug. Once the health care provider, pharmacy, or setting has met these requirements, they are referred to as “certified.” For health care providers who prescribe the drug, the process for obtaining this certification is referred to as “prescriber certification,” and for health care providers, pharmacies, and settings that dispense the drug, this process is referred to as “dispenser certification.”

²² For purposes of this guidance, REMS enrollment is the process by which participants provide basic identifying and demographic information to the REMS program, allowing the applicant to track and communicate with REMS participants.

²³ See section 505-1(f)(3)(D) of the FD&C Act.

²⁴ A comprehensive list of all REMS materials is also included at the end of the REMS document (See section III.E *REMS Materials* of this guidance).

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required if they might mitigate a serious adverse event occurring from abuse or overdose.²⁵

Requirements related to communication can include requirements for the applicant to develop materials about the REMS and/or the risks and safe use of the drug, and to disseminate the materials to health care professionals and professional organizations or societies. The following information should be included: the target audience, the type of materials to be disseminated, how the materials will be disseminated, the timing of the dissemination(s) and whether there is any follow-up required.

Requirements related to operations can include requirements for the applicant to develop, establish, and implement systems and infrastructure (e.g., databases, websites, call centers, distribution processes) to support the REMS requirements that enable access to and participation in the REMS.

Requirements related to compliance with the REMS can include requirements for the applicant to monitor and evaluate REMS participants' compliance with the REMS and address any noncompliance to ensure the REMS requirements are being met. For example, if a REMS includes a requirement for prescribers of a drug to complete training, the applicant is required to ensure that prescribers comply with the requirement to complete the training. These requirements include ensuring (e.g., through audits) that all REMS processes and procedures to support the REMS requirements are in place, functioning, and are being complied with.

D. REMS Assessment Timetable

The REMS Assessment Timetable section of the REMS document should describe the timetable for submission of assessments of the REMS by the applicant. REMS are generally required to include a timetable for submission of assessments, and applicants are required to submit assessments of the REMS at the specified intervals.²⁶

E. REMS Materials

The REMS Materials section should provide a comprehensive list of all the materials that are required for the REMS (e.g., enrollment forms, educational materials, counseling tools, monitoring forms, and patient-provider agreements). The list should be organized by the REMS participant(s) to which the materials apply and the type of REMS material.

F. Statutory Elements

The Statutory Elements section should provide a list of the elements, as outlined in section 505-1 of the FD&C Act, that FDA has determined are necessary to ensure that the benefits of the drug outweigh its risks. The list is organized by the order the element appears in the FD&C Act.

²⁵ See section 505-1(e)(4) of the FD&C Act.

²⁶ See section 505-1(d) of the FD&C Act.

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IV. PROCEDURES

A. Proposed REMS Submissions

Proposed REMS submissions should include two parts: the REMS (REMS document and REMS materials) and the REMS supporting document.

- REMS document and REMS materials:

The REMS document should use the format and content described in section III above. With the exception of the prescribing information and Medication Guide, the REMS materials should be appended to the REMS document. Foreign-language versions of REMS materials are not considered part of the approved REMS, and are not reviewed by FDA.^{27,28}

- REMS supporting document:

The REMS supporting document should expand on information in the REMS document, and provide additional information about the REMS, such as the rationale for and supporting information about the design, implementation, and assessment of the REMS (e.g., why a REMS is necessary based on application of the statutory factors,²⁹ how the REMS would ensure that the benefits of the drug outweigh the risks, implementation processes, compliance and enforcement policies and procedures, definitions, knowledge assessment analysis approach, and the REMS assessment plan).

Proposed REMS modifications to convert an already-approved REMS document to the new format should be submitted in accordance with the procedures outlined in the guidance for industry, *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (June 2020). FDA does not expect application holders of approved REMS to submit a proposed REMS modification solely to convert their REMS document to the new format. Changing the REMS document to the new format should be done in conjunction with other REMS modifications.^{30,31}

B. Submission Type

A proposed REMS can be included in the initial submission of an original or supplemental application (NDA, ANDA, and BLA), or submitted as an amendment to an existing original or supplemental application. All supplemental applications³² that include a new proposed REMS should be submitted as prior approval supplements. A proposed REMS submitted after product

²⁷ Consistent with CDER's approach to foreign-language labeling, when applicants distribute foreign-language versions of a currently approved REMS, applicants are responsible for ensuring that such materials are complete and accurate (see 21 CFR 201.15(c)).

²⁸ See manual of policies and procedures 6020.7 *Foreign Language Labeling* (October 2014).

²⁹ See guidance for industry *FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019).

³⁰ See guidance for industry *Providing Regulatory Submissions in Electronic Format – Content of Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling Format* (December 2020).

³¹ See guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (June 2020).

³² See 21 CFR 314.70, 314.97 and 601.12.

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approval and not associated with an existing supplemental application should be submitted as a new supplemental application.³³

C. Submission Identification

The first page of a proposed REMS submission should prominently identify the submission as **PROPOSED REMS** in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

When the proposed REMS is submitted as part of an original application:

**NDA/BLA/ANDA [assigned #]
NEW ORIGINAL APPLICATION FOR <name of drug>
PROPOSED REMS**

When the original proposed REMS is submitted as an amendment to an existing original or supplemental application:

PROPOSED REMS for NDA #####, ANDA #####, BLA #####

**PROPOSED REMS for NDA #####/S-000, ANDA #####/S-000, BLA ##### -
AMENDMENT**

When the original proposed REMS is submitted postapproval as a new supplemental application:

**NEW SUPPLEMENT FOR NDA #####/S-000, ANDA #####/S-000, BLA #####
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS**

When the original proposed REMS is submitted postapproval with a new supplemental application:

**NEW SUPPLEMENT FOR NDA #####/S-000, BLA #####
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS**

On the first page of subsequent submissions related to an already-submitted proposed REMS, prominently identify the submission by including this wording in bold capital letters at the top of the letter:

PROPOSED REMS for NDA #####, ANDA #####, BLA ##### -AMENDMENT

³³ For instructions on submission of REMS modifications, see the guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (June 2020).

D. Posting REMS Documents on the FDA Website

All approved REMS documents and their approved REMS materials are posted on FDA's website.³⁴ REMS supporting documents are not made available on FDA's website.

³⁴ Available at <https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>.