Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Guidance for Industry

The portion of this guidance document setting forth the submission procedures for risk evaluation and mitigation strategies revisions is being distributed for comment purposes only.

Comments and suggestions regarding this document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact (CDER) Kristen Everett at 301-796-0453, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-7800.

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)

April 2015
Drug Safety

Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Guidance for Industry

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TABLE OF CONTENTS

Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry[1]

This guidance represents the Food and Drug Administration's (the FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate the FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides information on how the FDA will define and process submissions from application holders[2] for modifications and revisions[3] to approved risk evaluation and mitigation strategies (REMS).[4] Specifically, this guidance provides information on what types of changes to REMS will be considered ***modifications*** of the REMS, as described in section 505-1(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and what types of changes will be considered ***revisions*** of the REMS.[5] There are different procedures for submission of REMS modifications and revisions to the FDA, as well as different time frames for FDA review and action on such changes. This guidance provides information on how REMS modifications and revisions should be submitted to the FDA, and the FDA's process for reviewing and acting on

[1] This guidance has been prepared by the Office of New Drugs, the Office of Surveillance and Epidemiology, and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Under section 505-1(b)(7) of the Federal Food, Drug, and Cosmetic Act, the term *responsible person* means "the person submitting a covered application or the holder of the approved such application." For ease of reference, this guidance refers to a responsible person as an *application holder*.

[3] The portion of this guidance setting forth the submission procedures for risk evaluation and mitigation strategies revisions is shaded in grey and is being distributed for comment purposes only.

[4] The REMS is the enforceable document that describes the elements that an application holder is required to implement to mitigate a specific, serious risk listed in the labeling of the drug. All proposed materials that are included as part of the REMS (e.g., communication and educational materials, Medication Guide, patient package insert, enrollment forms, prescriber and patient agreements) are also approved and enforceable, and are appended to the REMS document. This guidance refers to these materials as *appended REMS materials*.

[5] 21 U.S.C. 355-1(h)(2)(A)(iv)

these submissions. The definitions of REMS modifications and revisions set forth in this guidance apply to all types of REMS. This guidance is issued pursuant to sections 505-1(h)(2)(A)(ii), (iii), and (iv) of the FD&C Act.

This guidance does not address additional procedures that may apply to application holders proposing changes to REMS that are part of a single shared system.[6] The FDA intends to address these procedures in future guidance.

The information contained in this guidance pertaining to REMS modification and revision submission procedures for application holders and the time frames for the FDA review and action supersedes the information on the same topic contained in the draft guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the Agency's current thinking on major and minor modifications of REMS. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Insofar as this guidance establishes the modifications to an approved REMS that may be implemented following notification to the Secretary under section 505-1(h)(2)(A)(iv) — here referred to as REMS revisions — it has binding effect, except for the portions of the guidance setting forth the submission procedures for REMS revisions, which will, when final, have binding effect.

II. BACKGROUND

A REMS is a required risk management plan that uses tools beyond the prescribing information (the package insert) to ensure that the benefits of certain drugs outweigh their risks.[7] If the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks, the FDA is authorized to require a REMS for such drugs under section 505-1 of the FD&C Act,[8] added by section 901 of the Food and Drug Administration Amendments Act of 2007.[9] Sections 505-1(g) and (h) include provisions regarding the assessment and modification of an approved REMS. Section 1132 of the Food and Drug Administration Safety and Innovation Act

[6] See section 505-1(i)(1)(B) of the FD&C Act. A drug that is the subject of an abbreviated new drug application and the listed drug shall use a single shared system to implement the elements to assure safe use.

[7] For the purposes of this guidance, unless otherwise specified, references to *drugs* include drugs approved under the FD&C Act and biological products licensed under the Public Health Service Act (PHS Act), 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 applies to applications for prescription drugs submitted under FD&C Act subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications), and applications under section 351 of the PHS Act (i.e., biologics license applications).

[9] See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm.

(FDASIA) later amended the FD&C Act's provisions regarding changes to an approved REMS.[10]

An application holder may propose a REMS modification at any time. When the FDA determines that a modification of a REMS is necessary to ensure that the benefits of a drug outweigh its risks or to minimize the burden on the health care delivery system of complying with the REMS, the FDA has the authority to require submission of a proposed modification to a REMS under section 505-1(g) of the FD&C Act.

In 2009, the FDA issued draft guidance on the format and content of a REMS, REMS assessments, and proposed REMS modifications.[11] In that guidance, based on the language of sections 505-1(g) and (h) of the FD&C Act before the FDASIA amendments, the FDA stated that *any* proposed modification to an approved REMS, including proposed changes to materials that are appended to the REMS document, must be submitted as a proposed REMS modification in the form of a prior approval supplement (PAS), and must include a REMS assessment. The guidance states that the proposed modification(s) may not be implemented until approved by the FDA.

FDASIA amended the REMS modification provisions under section 505-1(g) and (h) of the FD&C Act. Section 505-1(h), as amended by FDASIA, requires the FDA to review and act on proposed *minor modifications*, as defined in guidance, within 60 days.[12] It also requires the FDA to establish, through guidance, that *certain modifications* can be implemented following notification to the FDA.[13] In addition, FDASIA requires the FDA to review and act on REMS modifications to conform the strategy to approved safety label changes, or to a safety label change that the FDA has directed the application holder make pursuant to section 505(o)(4) of the FD&C Act, within 60 days.[14] Finally, FDASIA specifies that proposed REMS modifications no longer require submission of a REMS assessment; instead, proposed modifications must include an adequate rationale for the proposed changes.

[10] See http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf.

[11] See the draft guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*.

[12] See section 505-1(h)(2)(A)(ii) of the FD&C Act.

[13] See section 505-1(h)(2)(A)(iv) of the FD&C Act. The FDA interprets *certain modifications* that can be implemented upon notification to the FDA to be changes to a REMS that are editorial in nature or appropriate for submission in an annual report, and therefore calls these REMS changes *revisions* to differentiate these changes from modifications that require the submission of a supplement and the FDA review and action.

[14] See section 505-1(h)(2)(A)(iii) of the FD&C Act.

Existing FDA regulations describe how to make changes to an approved new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA), and include a mechanism for rapid implementation of certain changes.[15] Some changes must be submitted as a PAS and approved before they are implemented; changes-being-effected (CBE) supplements may be implemented at the time they are submitted or 30 days following submission.[16] After review of a supplement, the FDA either approves the supplement (with any required modifications) or determines that it will not approve the supplement (i.e., issues a complete response letter). If the supplement was inappropriately submitted as a CBE, the FDA will notify the application holder that the proposed change(s) require FDA approval before implementation. A description of how these existing submission requirements apply to proposed REMS changes is provided in greater detail below.

III. POLICY

Changes to REMS will be categorized by the degree of their potential effect on the risk message (the information provided in the REMS about the serious risks or safe use of the drug) and/or other REMS requirements (e.g., the activities or other obligations of the application holder, patients, health care providers, and other stakeholders under the REMS). Table 1 in section III.A.2., List of REMS Revisions, shows changes that the FDA has determined do not affect the REMS risk message or other REMS requirements and will be considered REMS *revisions* (see definition below). Changes that potentially affect the REMS risk messages or other REMS requirements will be considered either minor or major REMS *modifications*; examples are provided in Tables 2 and 3 (section III.B.2., Examples of Minor and Major REMS Modifications), respectively.

The types of changes that potentially affect the risk message include those that augment, diminish, or alter the focus of the risk message or address an entirely new serious risk. The types of changes that potentially affect the REMS requirements include those that augment, minimize, or otherwise alter the REMS goals, elements, and tools,[17] and/or the actions application holders, patients, health care providers, and other stakeholders must take to comply with the REMS.

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[15] See 21 CFR 314.70 and 601.12.

[16] PAS-proposed changes must be approved by the FDA before implementation (21 CFR 314.70(b); 21 CFR 601.12(b)(3) and (f)(1)). CBE supplements contain changes that may be implemented by the application holder either immediately upon FDA receipt of the supplement (CBE-0 supplements) (21 CFR 314.70(c)(6) and 601.12(c)(5) and (f)(2)(ii)) or 30 days after FDA receipt of the supplement (CBE-30 supplements) (21 CFR 314.70(c) and 601.12(c)(3)).

[17] This guidance uses the phrase *REMS tool* to describe a process or system designed to implement one or more REMS elements. In some cases, an element itself, such as a Medication Guide, may be viewed as a tool. In other cases, such as an element to assure safe use that requires that a drug be dispensed to patients with evidence or other documentation of safe-use conditions, specific tools are used to implement a REMS element (e.g., systems to ensure that certain laboratory test result outcomes are obtained before a drug may be dispensed). See the draft guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*.

Proposed changes to approved REMS should be submitted as follows:

- *REMS revisions*, to be submitted as "REMS Revisions" *and* documented in the next annual report

  or

- *REMS modification*s, which are categorized as either:
  - *Minor*, to be submitted as a CBE-30 supplement
  - *Major*, to be submitted as a PAS

See section IV., Procedures, for more information about submission procedures.

A. REMS Revisions

1. Definition

REMS revisions are defined as being limited to editorial changes, corrections of typographical errors, and changes in the application holder name or address. These changes are changes to the REMS document and/or appended REMS materials that do not affect the risk message or other REMS requirements. A change to a Medication Guide that is an element of a REMS that meets the regulatory requirements for annual report submission also would be considered a REMS revision.[18] Submissions of REMS revisions are not supplemental applications and can be implemented following receipt of the submission by the FDA.

2. List of REMS Revisions

Table 1 provides a list of the changes to an approved REMS that will be considered to be REMS revisions. Changes to approved REMS that are not included in Table 1 will be considered REMS modifications.[19]

[18] See 21 CFR 208.20(b)(8)(iii), 21 CFR 208.20(b)(8)(iv), and the guidance for industry *Medication Guides — Adding a Toll-Free Number for Reporting Adverse Events*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[19] Application holders should contact the FDA if they have a proposed change that they believe should be a REMS revision but is not reflected in Table 1.

Table 1. REMS Revision (Submitted as REMS Revisions and Summarized in the Annual Report)[20]

Description[a]
Change in application holder name[b] *On the REMS document:* *NDA xx-xxx* *BRAND (established) name* *~~Original~~ New application holder name* *123 American Street* *Suite 445* *City, State 12345*
Updating the contact information (e.g., mailing address, telephone number, fax number, and/or email address) for the current application holder on the REMS document and/or the appended REMS materials *On the REMS document:* *NDA xx-xxx* *BRAND (established) name* *Original application holder name* *123 American Street* *Suite 445* *City, State 12345* *Phone (123) 456-~~7899~~ 1234*
Correcting grammatical, formatting, and/or typographical errors *"[DRUG] is associated with the potential ~~risk~~ risks of seizure and hepatotoxicity."*
Changing the application holder's signatory for a Dear Health Care Provider Letter that is part of the REMS communication plan materials *Dear Health Care Professional…* *[Body of letter]* *Sincerely,* *[Name],* *~~Senior Director, Medical Affairs~~ Senior Medical Director* *[Company]*

continued

[20] A summary of REMS revisions should be included under section c of the annual report (21 CFR 314.81(b)(2)(iii)(c)).

158 *Table 1, continued*

Description[a]
For REMS approved as a single shared system with a list of individual company names or drugs specified in the REMS: • Adding or removing the name of an application holder and/or new drug to the list in the REMS or REMS Web site[c] *Listed in REMS informational materials for prescribers:* *Drugs Covered Under This Program* *Drug name A* *Drug name B* ~~*Drug name C*~~ *New drug name D*
Adding or changing the proprietary or established drug name in the REMS document and/or appended REMS materials, if there are no other changes to the REMS program, and the FDA has agreed to the name change
Changing a trademark symbol, designated by ™, to the registered trademark symbol, designated by ®
Changes in the approved package count configuration that result in changes to the REMS appended materials (e.g., a change in the national drug code numbers listed in the appended materials)
The following changes to a Medication Guide that is an element of a REMS:[d] Changes in the application holder name and place of business[e] Inserting the date of the most recent revision of the Medication Guide[f] The addition of the side effects statement and toll-free number for reporting adverse events to a Medication Guide[g]

159 *continued*

Table 1, continued

Description[a]
The following changes to the timetable for submission of assessments: Revising the timetable for submission of assessments, to be consistent with the FDA's current standard language for the REMS timetable (as provided in the FDA's REMS document template) *[Company] will submit the [DRUG] REMS assessments ~~to the FDA~~ at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS (January 1, 2010).* For REMS involving multiple drugs in the same class and owned by the same application holder: Changing the timetable for submission of assessments of the REMS to synchronize the assessment due date(s) with those for other drugs in the class

[a] The types of REMS changes in italic font are provided for illustrative purposes. Additions are underlined; deletions are ~~struckthrough~~.
[b] Application holders are responsible for reporting a transfer of ownership in accordance with Federal regulations. The FDA must be notified in writing by the new and former application holders at the time of transfer in ownership of an NDA or BLA (21 CFR 314.72; 21 CFR 601.12(f)(1)). The REMS revision process only applies to updating the REMS to be consistent with a transfer of ownership previously reported.
[c] The REMS revision process can be used by the *previously existing* members of the single shared system REMS to add or remove an application holder or its drug, and only after that application holder's REMS is approved or is no longer required to be part of the single shared system.
[d] 21 CFR 314.70(b)(2)(v)(B) for NDAs and 21 CFR 601.12(f)(3)(C) for BLAs
[e] 21 CFR 208.20(b)(8)(iii)
[f] 21 CFR 208.20(b)(8)(iv)
[g] See the guidance for industry *Medication Guides — Adding a Toll-Free Number for Reporting Adverse Events*.

B. REMS Modifications

1. Definition

As stated above, changes to approved REMS will be categorized by the degree of their potential effect on the risk message and/or the REMS requirements. Proposed REMS modifications are divided into two categories: minor modifications and major modifications.

1. *Minor modifications* are defined as changes that may nominally affect the risk message, and/or nominally change the REMS requirements[21] and are submitted as a CBE-30 supplement

[21] A minor modification corresponds to a "moderate change" under 21 CFR 314.70(c)(1).

2. *Major modifications* are defined as changes that may substantially affect the risk message, and/or substantially change the REMS requirements[22] and are submitted as a PAS

Proposed changes to approved REMS that are not listed in Table 1 will be considered REMS modifications.

2. Examples of Minor and Major REMS Modifications

Tables 2 and 3 provide examples of changes to approved REMS that will be considered to be minor and major REMS modifications, respectively. These examples are intended to be representative, rather than a comprehensive list of all kinds of minor and major REMS modifications.

Table 2. Minor REMS Modifications (Submitted as CBE-30 Supplements)

Type of Change	**Examples**[a]
Nominal changes to the REMS requirements or associated processes under the REMS	*In the REMS document for an antihypertensive agent:* *"The mailing list for the Dear Health Care Professional Letter will consist of health care ~~of any specialty~~ providers in the field of cardiology who wrote at least one prescription for [DRUG] within the past 2 years."* *In the REMS document for a REMS with ETASU:** *[Company] will maintain a database of certified prescribers in the REMS program. [Company] will ~~ensure that~~ monitor the database to ascertain that prescribers' certification requirements are met.* Expanding the enrollment process to include online registration, in addition to enrollment via email or fax Creation of a new enrollment form that is similar in content to the currently approved enrollment form, to accommodate existing processes within closed health care systems Changing the health care provider enrollment form(s) to collect an additional piece of demographic data such as a prescriber's medical specialty, or providers' unique identifier

continued

[22] A major modification corresponds to a "major change" under 21 CFR 314.70(b).

Table 2, continued

Type of Change	Examples[a]
Changes to the REMS document and/or appended REMS materials that may nominally affect the risk message, including the presentation of the risk message	Addition of an approved new strength or dosage form of the drug to the REMS document and/or the appended REMS materials Removal of a strength or dosage form from the REMS document or the appended REMS materials (other than the Medication Guide), because either approval has been withdrawn and documented by publication of a *Federal Register* notice for the strength/dosage form or the FDA has determined that the strength/dosage form was withdrawn from sale for reasons of safety or effectiveness Adding, removing, or otherwise changing information about other drugs mentioned in the appended REMS materials (i.e., not the drug for which the REMS was required) • Adding a new, recently approved drug to a class of drugs already mentioned in the appended REMS materials, such as a new drug to a list of drugs that can cause a drug-drug interaction Re-ordering the risk information in the appended REMS materials Changes to graphics in the appended REMS materials, including changing the manufacturer's logo or the logo for the REMS program

[a] The types of REMS changes in italic font are provided for illustrative purposes. Additions are underlined; deletions are ~~struckthrough~~.

* ETASU = element to assure safe use

Table 3. Major REMS Modifications (Submitted as a PAS)

Type of Change	Examples[a]
Any change to the REMS goal(s)	Addition, removal, or change to a REMS goal *Original goal: "To reduce the risk of misuse…"* *Revised goal: "To reduce the risk of abuse and misuse…"*
Addition, removal, or other major changes to a REMS element, including the timetable for submission of assessments of the REMS	Changes to the timetable for submission of assessments of the REMS that alter the frequency and/or number of the assessments Changes to an ETASU to modify the verification process required before the drug will be dispensed to patients* Removing the Medication Guide as an element of the REMS

continued

210 *Table 3, continued*

Type of Change	**Examples**[a]
Addition, removal, or other major changes to a REMS tool described in the REMS document and/or appended REMS materials	Adding a new letter to health professional societies to the communication plan Removing the REMS Web site from the communication plan or an ETASU Changing the prescriber enrollment form to remove an attestation that the prescriber understands the serious risk(s) of the drug Adding or removing a prescriber educational tool, such as a slide deck or safety information brochure Changes to patient demographic or other identifying information collected in the enrollment forms or otherwise reflected in the appended REMS materials
Changes to the REMS document and/or appended materials that may substantially affect the risk message, and/or substantially change the REMS requirements	Addition of new safety information about the serious risks associated with the drug that are already included in the REMS Changes to reflect expansion of the patient population based on approval of a new indication Changes related to drug administration that affect patient safety Changes to reflect a change in the frequency and/or timing of patient laboratory testing required to ensure documentation of safe-use conditions
Changes that may substantially affect the presentation of the risk message	Changing the name of the REMS program to add or remove wording that affects the risk message *Original name: [Established drug name] REMS Program* *New name: [Established drug name] Access and Training REMS Program*
Any change to a Medication Guide that is an element of a REMS *and* for which the FDA approval of the changes is required[b]	Any change to a Medication Guide not described under Table 1 must be submitted in a PAS, unless the changes are appropriate for submission in a CBE-0 supplement, or the application holder has been granted a waiver of the PAS submission requirement under 21 CFR 314.90[c]
Modification to release the REMS requirement	Modification that proposes to remove all remaining elements from a REMS, and thus release the REMS requirement entirely

211 *continued*

Table 3, continued

Type of Change	Examples[a]
Modifications due to safety labeling changes	Changes to the content of the *Prescriber Safety Information Brochure* and *Pharmacy Safety Information Brochure* to reflect safety label changes made to the WARNINGS and PRECAUTIONS sections of the product label

[a] The types of REMS changes in italic font are provided for illustrative purposes. Additions are underlined; deletions are ~~struckthrough~~.
[b] 21 CFR 314.70(b)(2)(v)(B) and 601.12(f)(1)
[c] 21 CFR 314.70(c)(6)(iii)(E) and 314.90
* ETASU = element to assure safe use

IV. PROCEDURES

A. General Considerations

Submissions containing REMS revisions and/or proposed REMS modifications should include a detailed description of the REMS changes. All proposed REMS modifications initiated by the application holder (minor or major) also must be accompanied by an adequate rationale for the proposed change(s).[23] This allows the FDA to determine quickly if the appropriate submission category has been used.

In addition, to assist the FDA with tracking submissions of REMS revisions and modifications, it is recommended that application holders include a REMS history that outlines all changes made to the REMS since its approval. 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 label. The REMS history should be in a tabular format that captures all approved and/or pending changes to the REMS to date (revisions, minor modifications, and major modifications). The REMS history should 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 pending modifications) or approval; or, in the case of REMS revisions, the date of receipt by the FDA.

When the FDA requires submission of proposed changes to an application holder's REMS,[24] the FDA will specify the types of changes required and the type of submission that is needed (CBE-30 supplement or PAS).

The Electronic Submissions Gateway Web site[25] provides email addresses that application holders can use for questions about electronic submissions (e.g., location of REMS materials in the electronic common technical document) and general questions about sending electronic

[23] See section 505-1(g)(4)(A) of the FD&C Act.

[24] See section 505-1(g)(4)(B) of the FD&C Act.

[25] See http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm.

submissions through the electronic submissions gateway. Application holders also can refer to the draft guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations*.[26]

B. Submission Procedures for REMS Revisions

Application holders should identify a REMS revision submission with the following wording in bold capital letters on the top of the first page of the submission:

REMS REVISION

A REMS revision submission should include the following:

- A detailed description of the changes to the REMS and/or appended materials, the date the changes will be implemented, and a REMS history as described above
- Clean Word versions of the revised REMS and all appended REMS materials
- A redlined (track changes) Word version of the revised REMS and revised appended REMS materials that shows the changes from the previous versions
- A single PDF file that includes clean versions of the REMS document and all appended materials
- An updated REMS Supporting Document to align with changes made to the REMS document and REMS appended materials, as appropriate
- Specification on Form FDA 356h, under *Item 21 Submission: Other (Specify)*, that the submission contains a "REMS Revision"

Additionally, REMS revisions should be documented in the next annual report for the application.[27] Because REMS revisions are not submitted as supplemental applications, they do not require FDA action, and can be implemented following receipt by the FDA.

All subsequent REMS submissions (i.e., proposed minor or major modifications or additional REMS revisions) should include previously implemented REMS revisions in the REMS document and appended materials, and should be noted in the REMS history.

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

[27] A summary of REMS revisions should be included under section c of the annual report (21 CFR 314.81(b)(2)(iii)(c)).

C. Submission Procedures for REMS Modifications

Proposed minor modifications to a REMS should be submitted to the application as a CBE-30 supplement, and proposed major modifications should be submitted as a PAS. All submissions containing proposed modifications (either minor or major) must include a detailed description of the changes and an adequate rationale for the changes being proposed.[28] However, an adequate rationale is not needed when the FDA requires submission of a proposed modification under section 505-1(g)(4)(B) of the FD&C Act.

An adequate rationale for the proposed REMS modification must include the appropriate information to support the proposed change(s).[29] This may include, but is not limited to, the reason(s) why the proposed modification is necessary; the potential effect of the proposed modification on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. If a REMS assessment was submitted in the past 18 months and includes data to support the proposed change, then it can be referenced as the adequate rationale.

If a proposed REMS modification is submitted as part of an efficacy supplement for a new indication of use, the REMS assessment that is required in accordance with section 505-1(g)(2)(A) of the FD&C Act will be considered the adequate rationale to support the proposed REMS modification.

Proposed REMS modifications due to approved safety label changes or to a safety label change that the FDA has ordered the holder of an application to make pursuant to section 505(o)(4) of the FD&C Act are considered major modifications and should be submitted as a PAS, but they are subject to a different time frame for review (see section IV.D., Time Frames for Review of, and Action on, REMS Modifications). The FDA recommends such REMS modifications be submitted at the same time as the proposed labeling changes, but in a separate supplement, to allow the requisite time for the FDA to review and take action. These types of REMS modification submissions also should include an adequate rationale. However, the rationale may consist of a statement that the REMS changes are submitted due to the approved or ordered safety label changes.

We encourage application holders to, when possible, submit multiple proposed REMS modifications of the same type in a single submission, either in a CBE-30 supplement or a PAS, as appropriate. Additionally, a new proposed REMS modification supplement (either a CBE-30 or PAS) should reference any other pending proposed REMS modifications.

Application holders should identify a proposed REMS modification submission with the applicable following wording in bold capital letters on the top of the first page of the submission:

[28] See section 505-1(g)(4) of the FD&C Act.

[29] See section 505-1(g)(4)(A) of the FD&C Act.

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
CHANGES BEING EFFECTED IN 30 DAYS
< other supplement identification >
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
PRIOR APPROVAL SUPPLEMENT
< other supplement identification >
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
PRIOR APPROVAL SUPPLEMENT
< other supplement identification >
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

All proposed REMS modification submissions (minor or major, including modifications due to safety labeling changes) should include the following:

- A detailed description of the changes to the REMS and/or appended REMS materials and a REMS history as described above
- An adequate rationale for the proposed modifications (or, appropriate reference to a REMS assessment performed in the past 18 months; see the discussion of an adequate rationale above), if required
- A clean Word version of the modified REMS and all appended REMS materials
- A redlined (track changes) Word version of the modified REMS and modified appended REMS materials that shows the changes from the previous versions
- An updated REMS Supporting Document to align with changes made to the REMS document and REMS appended materials, including updates to the REMS assessment plan, as appropriate
- Specification on Form FDA 356h, under *Item 21 Submission*, that the submission is a REMS Supplement, and the type of supplement under *Item 23*

D. Time Frames for Review of, and Action on, REMS Modifications

The FDA will promptly assess submissions that contain proposed REMS modifications to determine whether the proposed changes meet the criteria for the type of submission used (i.e.,

CBE-30 for minor REMS modifications or a PAS for major REMS modifications, including REMS modifications due to safety label changes). If the FDA determines that the REMS changes are not appropriately submitted, the FDA will do the following:

- For major modifications inappropriately submitted as minor modifications in CBE-30 supplements:
  - Notify NDA/BLA application holders within 30 days of submission that the changes are considered major modifications that require FDA approval before implementation
  - Notify ANDA application holders within 30 days of submission to withdraw the CBE-30 supplement and resubmit the proposed REMS modification as a PAS with the appropriate user fee[30]
- For REMS modifications submitted as major modifications in PAS, including modifications due to safety labeling changes:
  - If the FDA determines that the proposed changes do not require FDA approval before implementation, change the submission type accordingly and notify the application holder in writing of the change

For minor modifications, if the FDA informs the application holder within 30 days of receipt of the CBE-30 supplement that information necessary to act on the submission is missing, implementation of the modified REMS should be delayed until the supplement has been amended to provide the missing information. If the missing information is not received in time to allow for an adequate review of the CBE-30 supplement, the FDA may issue a complete response letter.

For REMS modifications appropriately submitted as minor modifications in CBE-30 supplements, the FDA will review and act on the proposed changes no later than 60 days from receipt of the proposed modifications.[31] Although the application holder can implement the modified REMS 30 days after receipt by the FDA, the changes to the REMS are not considered final until approved by the FDA.

For REMS modifications appropriately submitted as major modifications in a PAS, the FDA will review and act on the proposed changes within 180 days of receipt of the proposed modifications.[32]

[30] See 21 U.S.C. 379j-42(a)(3).

[31] See section 505-1(h)(2)(A)(ii) of the FD&C Act.

[32] See section 505-1(h)(2)(A)(i) of the FD&C Act. The 180-day review time frame does not apply if the dispute resolution process under paragraph (3) or (4) applies.

For a proposed REMS modification due to approved safety label changes or to label changes that the FDA has ordered the application holder to make under section 505(o)(4) of the FD&C Act, the FDA will review and act on proposed conforming REMS modification within 60 days of receipt of the modification. The FDA interprets REMS modifications that *conform* to safety label changes in section 505-1(h)(2)(A)(iii) of the FD&C Act to refer to modifications that transfer the newly approved label language into the existing REMS and/or appended REMS materials. Overall design, programmatic, and/or implementation changes to the REMS that result from approved (or ordered) safety label changes are *not considered conforming* REMS modifications; the FDA will review and act on these modifications within 180 days. Proposed major REMS modifications, including modifications to due to safety label changes, must not be implemented before FDA approval.[33]

As stated in section IV.C., Submission Procedures for REMS Modifications, the FDA encourages application holders to submit multiple REMS changes of the same type in a single submission. However, because the FDA takes one action per supplement, submissions that contain REMS changes of different types (e.g., REMS revisions and minor modifications, or minor modifications and major modifications) will be reviewed and acted upon based on the time frame for the longer review clock. Therefore, submissions that include both minor and major REMS modifications will be reviewed and acted upon within 180 days of receipt to allow sufficient time for review of the major modifications. Submissions containing both minor modifications and REMS revisions will be reviewed and acted upon within 60 days to allow sufficient time for review of the minor modifications.

Proposed REMS modifications that are submitted together with a REMS assessment that is required in accordance with the timetable for submission of assessments of the REMS will be reviewed concurrently. Action on the proposed REMS modifications will follow review of the REMS assessment.

Proposed REMS modifications submitted or required as part of an efficacy or chemistry, manufacturing, and controls supplement will be reviewed and acted on as part of that supplement, and not according to the time frames described above for REMS revisions, minor modifications, or major modifications.[34] REMS changes submitted as part of an efficacy or chemistry, manufacturing, and controls supplement may not be implemented until approved.

[33] See 21 CFR 314.70(b)(3). It is the FDA's view that the labeling changes process under 21 CFR 314.70 and 601.12 continues to be available to application holders in situations in which the application holder becomes aware of newly acquired information, including in circumstances that meet the criteria for submission of a *supplement — changes being effected* (CBE-0).

[34] For more information on the FDA's review of efficacy supplements, see the guidance for industry *Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements*. For more information on the FDA's review of chemistry, manufacturing, and controls supplements, see the guidance for industry *Changes to an Approved NDA or ANDA*.

E. Posting Revised and Modified REMS on the FDA Web Site

All approved REMS and their appended materials are posted on the FDA's Web site.[35]

The FDA intends to post updated REMS reflecting REMS revisions on the Web site within 14 days of receipt of the submission.

For proposed REMS modifications submitted as either CBE-30 or PAS supplements, the FDA intends to post the REMS and appended materials on the Web site generally within 3 days of approval.

V. CONTACT INFORMATION

The primary contacts for questions about a proposed REMS revision or modification are as follows.

In CDER:

- For a drug under an NDA or BLA: the regulatory project manager in the Office of New Drugs (OND) review division responsible for that drug

- For a drug under an ANDA: the regulatory project manager in the Division of Project Management, Office of Regulatory Operations, in the Office of Generic Drugs (OGD)

CDER's Office of Surveillance and Epidemiology, and other program offices as needed, will work with OND and OGD in the review of a proposed REMS modification.

In the Center for Biologics Evaluation and Research (CBER):

- The regulatory project manager in the office responsible for that drug

CBER's Office of Biostatistics and Epidemiology, and other program offices as needed, will work with the appropriate drug office in the review of a proposed REMS modification.

[35] See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm.