Changes to an Approved REMS
an Introduction to the
Risk Evaluation & Mitigation Strategies:
Modifications & Revisions
Guidance for Industry

FDA Webinar

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Center for Drug Evaluation and Research

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Changes to an Approved REMS
an Introduction to the
*Risk Evaluation & Mitigation Strategies: Modifications & Revisions* Guidance for Industry
RISK EVALUATION AND
MITIGATION STRATEGIES:
MODIFICATIONS AND REVISIONS
GUIDANCE FOR INDUSTRY

The portion of this guidance document setting forth the submission procedures for REMS revisions is being distributed for comment purposes only.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be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance.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.
Outline

Part I: Background & Policy (Moncur)

• Historical Overview
• Categorizing Risk Evaluation and Mitigation Strategy (REMS) Changes
• Adequate Rationale

Part II: Procedures (Everett)

• Submission and Review of Each Type of REMS Change
• Combination Submissions
Learning Objectives

• Understand ‘changes to an approved REMS’ before and after FDASIA

• Understand the different categories of REMS changes in the guidance

• Understand application holder submission procedures for the different types of REMS changes

• Understand FDA’s process for reviewing and acting on different types of REMS changes
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Notable REMS Milestones

- 2007 FDAAA\textsuperscript{a}
- 2009 Format & Content Draft Guidance \textsuperscript{b}
- 2010 REMS Public Meeting
- 2012 FDASIA\textsuperscript{c}
- 2015 Modification & Revision Guidance \textsuperscript{d}

\textsuperscript{a} Section 901 of the Food & Drug Administration Amendments Act (FDAAA) of 2007
\textsuperscript{b} Draft Guidance for Industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*
\textsuperscript{c} Section 1132 Food & Drug Administration Safety and Innovation Act (FDASIA) of 2012
\textsuperscript{d} Guidance for Industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*
Overview of REMS Modification Provisions, as Amended by FDASIA

• Identified different types of REMS changes and directed FDA to issue guidance

• Specified timeframes for FDA review and action

• Established a new standard for when FDA can require an applicant to submit a proposed modification

• Changed what applicants are required to include in a submission proposing modifications to a REMS
Pre-FDASIA: Policy on Changes to REMS

| 1. REMS Change Types/ Categories | • Any proposed change to an approved REMS is a modification  
• Submitted as a prior approval supplement (PAS) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Action Time Frame</td>
<td>Within 180 days of receipt</td>
</tr>
<tr>
<td>3. When can FDA require a REMS modification?</td>
<td>If there is new safety information</td>
</tr>
<tr>
<td>4. What is an applicant required to include in a proposed modification submission?</td>
<td>A REMS assessment</td>
</tr>
</tbody>
</table>

^ Refer to section 505-1(b)(3) of the FD&C Act
<table>
<thead>
<tr>
<th>Post-FDASIA: Policy on Changes to REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. REMS Change Types/Categories</strong></td>
</tr>
<tr>
<td>- Multiple types of changes/categories:</td>
</tr>
<tr>
<td>- Revisions</td>
</tr>
<tr>
<td>- Minor Modifications</td>
</tr>
<tr>
<td>- Major Modifications</td>
</tr>
<tr>
<td>- Modifications due to Safety Labeling Changes</td>
</tr>
<tr>
<td>- Multiple submission types, that align with the different REMS change types</td>
</tr>
<tr>
<td><strong>2. Action Time Frame</strong></td>
</tr>
<tr>
<td>Time frames align with the different submission types</td>
</tr>
</tbody>
</table>
### Post-FDASIA: Policy on Changes to REMS

<table>
<thead>
<tr>
<th>3. When can FDA require a REMS modification?</th>
<th>When FDA determines that the REMS should be modified to ensure benefits &gt; risks, or to minimize the burden on the health care delivery system of complying with the REMS&lt;sup&gt;a&lt;/sup&gt; (New safety information is no longer required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. What is an applicant required to include in a proposed modification submission?</td>
<td>An adequate rationale&lt;sup&gt;b&lt;/sup&gt; (Assessment no longer required)</td>
</tr>
</tbody>
</table>

<sup>a</sup> See section 505-1(g)(4)(B)(ii) and (iii) of the FD&C Act

<sup>b</sup> See section 505-1(g)(4)(A) of the FD&C Act
## Policy Summary

### Changes to an Approved REMS Before & After FDASIA

<table>
<thead>
<tr>
<th>Pre-FDASIA</th>
<th>Post-FDASIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>All</em> proposed changes are modifications and require a PAS</td>
<td>Multiple change categories: <em>revisions</em>, <em>minor &amp; major modifications</em>, and <em>modifications due to SLCs</em>, with corresponding submission types</td>
</tr>
<tr>
<td>180-day review clock</td>
<td>Each submission type has a corresponding review clock</td>
</tr>
<tr>
<td>FDA needs new safety information to require a modification</td>
<td>When FDA determines that the REMS should be modified to ensure benefits &gt; risks, or to minimize the burden on the health care delivery system of complying with the REMS</td>
</tr>
<tr>
<td>Applicant must include a REMS assessment when proposing modifications to a REMS</td>
<td>Applicant must include an <em>adequate rationale</em> when proposing modifications to a REMS</td>
</tr>
</tbody>
</table>
Outline

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• Historical Overview

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Part II: Procedures

• Submission and Review of Each Type of REMS Change

• Combination Submissions
REMS Changes are Categorized by their Potential Effect on REMS Risk Messages and/or Requirements

• The REMS risk message is:
  • The information provided in the REMS about the serious risks or safe use of the drug

• Changes that potentially impact a risk message include those that:
  • Augment, diminish or alter the focus of the risk message
  • Address an entirely new serious risk
REMS Changes are Categorized by their Potential Effect on REMS Risk Messages and/or Requirements

• REMS requirements are:
  • Activities or other obligations of the applicant, patients, healthcare providers, or other stakeholder under the REMS

• Changes that potentially affect the REMS requirements include those that:
  • Augment, diminish or alter the REMS goals, elements or tools, and/or the actions a patient, healthcare provider, applicant or other stakeholder must take to comply with the REMS.
## REMS Revisions vs. REMS Modifications

<table>
<thead>
<tr>
<th>Change Category</th>
<th>Potential effect on REMS risk messages and/or requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revisions(^a)</td>
<td>No effect (e.g. editorial in nature)</td>
</tr>
<tr>
<td>Modifications</td>
<td>Have an effect</td>
</tr>
</tbody>
</table>

\(^a\) See section 505-1(h)(2)(A)(iv) of the FD&C Act.
Overview of REMS Change Categories

<table>
<thead>
<tr>
<th>Change Category</th>
<th>Potential effect on REMS risk messages and/or requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revisions</td>
<td>No effect</td>
</tr>
<tr>
<td>Modifications:</td>
<td></td>
</tr>
<tr>
<td>Minor Modification (^a)</td>
<td>Nominal</td>
</tr>
<tr>
<td>Major Modification</td>
<td>Substantial</td>
</tr>
<tr>
<td>Modification due to Safety Labeling Changes (^b)</td>
<td>Substantial</td>
</tr>
</tbody>
</table>


\(^b\) See section 505-1(h)(2)(A)(iii) of the FD&C Act.
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Adequate Rationale a

- **What is it?**
  - ‘Appropriate’ information to support the application holder’s proposed change(s) to the REMS
  - May include, but is not limited to
    - Reason(s) why the REMS modification is necessary
    - Potential effect of the modification on the: serious risks targeted by the REMS, patient access to the drug, and/or burden on health care delivery system
    - Other appropriate evidence/data

\[a\] See section 505-1(g)(4)(A) of the FD&C Act.
Adequate Rationale

• **When is it required?**
  
  • With all proposed modifications (major or minor), initiated by the application holder

• **When is it not required?**
  
  • REMS Revisions are not considered modifications, so an adequate rationale is not needed
  
  • If FDA requires submission of a proposed modification, the applicant does not need an adequate rationale
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Submission and Review of Each Type of REMS Change

Revisions

Minor Modifications

Major Modifications

Modifications Due to Safety Labeling Changes
REMS Revisions: Policy & Definition

• These changes do not affect the risk message or other REMS requirements

• Limited to editorial changes, corrections of typographical errors, and changes in the application holder name or address, certain changes to Medication Guides

• There are only 10 changes that are considered revisions – See Table 1 in the guidance
REMS Revisions: 
Table 1 in the Guidance

If a proposed change is not in Table 1, the change will be considered a REMS modification.
REMS Revisions: Application Holder Procedures

• Can submit as a *REMS Revision*
  • Can identify the submission in bold capital letters on the top of the first page
  • Documented in the next annual report for the application

• Submission can include the following:
  • REMS History and detailed description of the changes to the REMS
  • Redlined and clean versions of the REMS document and appended materials in Word format
  • A single PDF file that includes clean version of the REMS document and all appended materials
  • Updated REMS Supporting Document, if appropriate
<table>
<thead>
<tr>
<th>Change No. (type of change)</th>
<th>Date Submitted</th>
<th>Date Approved or Implemented</th>
<th>Documents Affected</th>
<th>Overview of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>01/01/2015</td>
<td>10/01/2015</td>
<td>Original REMS</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1 (Major Mod)</td>
<td>02/22/2016</td>
<td>08/08/2016</td>
<td>• REMS</td>
<td>Modified to address the addition of permanent AF to the Contraindications Section of the Prescribing Information</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Prescriber Enrollment Form</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• FAQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Supporting Document</td>
<td></td>
</tr>
<tr>
<td>2 (Revision)</td>
<td>12/06/2016</td>
<td>12/06/2016</td>
<td>• Prescriber Brochure</td>
<td>Fix typos</td>
</tr>
<tr>
<td>3 (Minor Mod)</td>
<td>04/14/2017</td>
<td>pending</td>
<td>• Pharmacy Enrollment Form</td>
<td>Add field for name of back-up pharmacist-in-charge</td>
</tr>
</tbody>
</table>
REMS Revisions: FDA Procedures

- REMS Revision submissions:
  - Are not supplements, therefore no approval is needed
  - Can be implemented upon receipt by FDA
- FDA will inform the application holder if the proposed changes do not meet the criteria for REMS revisions
- The revised REMS will be posted on the FDA website for Approved REMS

Submission and Review of Each Type of REMS Change

Revisions

**Minor Modifications**

Major Modifications

  Modifications Due to Safety labeling Changes
Minor REMS Modifications: Policy and Definition

- Changes that may \textit{nominally} affect the risk message, and/or \textit{nominally} change the REMS requirements

- Refer to Table 2 in the guidance for a list of examples of minor REMS modifications
Minor REMS Modifications: Application Holder Procedures

• Submit as a *CBE-30 Supplement*
  
  • Identify the submission in bold capital letters on the top of the first page:

  NEW SUPPLEMENT FOR NDA/BLS/ANDA
  CHANGES BEING EFFECTED IN 30 DAYS
  PROPOSED MINOR REMS MODIFICATION

• Submission should include the following:
  
  • REMS History and detailed description of the changes to the REMS
  
  • For modifications initiated by the application holder, an adequate rationale to support the modifications
  
  • Redlined and clean versions of the REMS document and appended materials in Word format
  
  • Updated REMS Supporting Document, if appropriate
Minor REMS Modifications: FDA Procedures

• FDA will review and act on a CBE-30 Supplement: Minor REMS Modifications within 60 days of receipt
  • Changes can be implemented within 30 days of receipt by FDA, but are not final until approved

• If the proposed REMS changes do not meet the criteria for minor modifications, FDA will inform the application holder within 30 days that supplement type has been changed

• The approved modified REMS will be posted on the FDA website for Approved REMS
Submission and Review of Each Type of REMS Change

Revisions

Minor Modifications

Major Modifications

Modifications Due to Safety Labeling Changes
Major REMS Modifications: Policy and Definition

- Changes that may substantially affect the risk message, and/or substantially change the REMS requirements

- Please refer to Table 3 in the guidance for a list of examples of major REMS modifications
Major REMS Modifications: Application Holder Procedures

• Submit as a *Prior Approval Supplement*
  • Identify the submission in bold capital letters on the top of the first page:
    
    NEW SUPPLEMENT FOR NDA/BLS/ANDA PRIOR APPROVAL SUPPLEMENT PROPOSED MAJOR REMS MODIFICATION
  
• Submission should include the following:
  • REMS History and detailed description of the changes to the REMS
  • For modifications initiated by the application holder, an adequate rationale to support the modifications
  • Redlined and clean versions of the REMS document and appended materials in Word format
  • Updated REMS Supporting Document, if appropriate
Major REMS Modifications: FDA Procedures

- FDA will review and act on a Prior Approval Supplement: Major REMS Modifications within 180 days of receipt
  - Changes may not be implemented until approved
- If the proposed REMS changes do not meet the criteria for major modifications, FDA will inform the application holder that supplement type has been changed
- The approved modified REMS will be posted on the FDA website for Approved REMS
Submission and Review of Each Type of REMS Change

Revisions

Minor Modifications

Major Modifications

Modifications Due to Safety Labeling Changes
Modifications Due to Safety Labeling Changes: Policy and Definition

• REMS modifications based on approved or ordered safety labeling changes
  • Safety labeling changes include those the application holder initiates under current regulations (including in a CBE-0 supplement) and those labeling changes the FDA requires under 505(o)(4)

• Safety labeling changes can result in:
  • Conforming REMS modifications – changes that transfer the newly approved or ordered labeling language into the REMS
  • Changes that also trigger the need for overall REMS design, programmatic, and/or implementation changes will not be considered as conforming
REMS Modifications Due to Safety Labeling Changes: Application Holder Procedures

• Submit as a *Prior Approval Supplement*
  
  • Identify the submission in bold capital letters on the top of the first page:

  NEW SUPPLEMENT FOR NDA/BLS/ANDA
  PRIOR APPROVAL SUPPLEMENT
  PROPOSED MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

• May be submitted *before or after* the safety labeling changes have been approved or ordered

• Should be submitted in a *separate supplement* than the labeling changes
REMS Modifications Due to Safety Labeling Changes: Application Holder Procedures

• Submission should include the following:
  • REMS History and description of changes to the REMS
  • Redlined and clean versions of documents
  • Updated REMS Supporting Document, if needed
  • An adequate rationale to support the changes
    - Can be a statement that the proposed modifications are due to the safety labeling changes
REMS Modifications Due to Safety Labeling Changes: FDA Procedures

- FDA will review and act on conforming Modifications Due to Safety labeling Changes within 60 days
- FDA will review and act on changes not considered conforming within 180 days
  - Timeframe for review does not begin until the labeling changes have been approved or ordered and FDA has received the modifications that align with the labeling changes
  - Changes may not be implemented until approved
- The approved modified REMS will be posted on the FDA website for Approved REMS
## Summary of REMS Changes

<table>
<thead>
<tr>
<th>Timeframe for Review</th>
<th>REMS Mods Due to SLCs*</th>
<th>REMS Mods Due to All Other Reasons</th>
<th>Editorial changes only</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-day</td>
<td>Conforming (PAS)</td>
<td>Minor Modification (CBE-30)</td>
<td></td>
</tr>
<tr>
<td>180-day</td>
<td>Not considered conforming (PAS)</td>
<td>Major Modification (PAS)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td>REMS Revision</td>
</tr>
</tbody>
</table>

*SLCs: Significant Label Changes
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Submissions Containing More Than One Type of REMS Change

Because FDA takes one action per supplement, submissions that contain more than one type of proposed REMS change will be reviewed according to the proposed change that has the longer review time frame.
Submissions Containing More Than One Type of REMS Change

• If submission includes both minor and major modifications and/or REMS revisions, FDA will review and act in 180 days

• If submission includes both minor modifications and REMS revisions, FDA will review and act in 60 days

• The application holder can resubmit REMS revisions in a separate submission if they need to be implemented immediately.
Submissions Containing REMS Modifications and…

- **REMS Assessment** - modifications reviewed concurrently with assessment and acted on when assessment review is complete

- **Efficacy or CMC supplement** – modifications reviewed and acted on as part of the supplement

In either case, modifications may not be implemented until approved
References

• Section 505-1 of the FDCA (i.e., REMS provisions):

• Link to *Format and Content of REMS* guidance:

• Link to FDA Approved REMS website:

• Link to FDA REMS Public Meeting, July 2010 transcripts:
  http://www.fda.gov/Drugs/NewsEvents/ucm210201.htm
Thank You!
Contact Information

If you have any questions please contact CDER Small Business and Industry Assistance (SBIA) at:

• Email: CDERSBIA@fda.hhs.gov

• Tel: 1-301-796-6707
   1-866-405-5367

• Website: www.fda.gov/cdiersbia