Risk Evaluation and Mitigation Strategies (REMS) for Generic Drugs: Use of a Drug Master File (DMF) and REMS Modifications

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U.S. Food and Drug Administration
SBIA Generic Drugs Forum 2023

Learning Objectives

What is a REMS?

- Define a REMS and REMS requirements

REMS with a DMF

- Explain the differences and similarities of REMS with and without a DMF

REMS Revisions and Modifications

- Define REMS revisions and modifications and submission requirements for pending versus approved Abbreviated New Drug Applications (ANDAs)

What is a REMS?

The Food and Drug Administration Amendments Act (FDAAA) of 2007, under Section 901 requires applicants to:

1. Develop and comply with REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

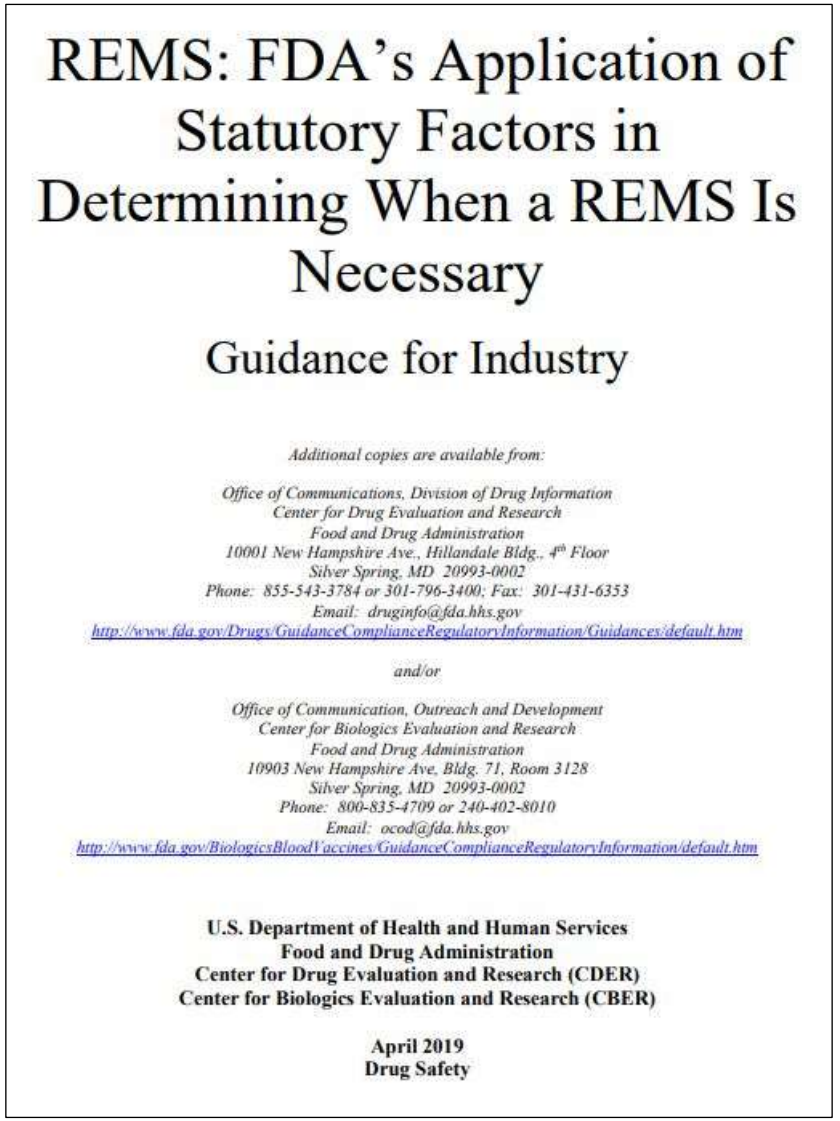
2. Develop a risk management plan beyond the labeling to ensure the benefits of a drug outweigh known risks.

3. Generally, focuses on communicating to patients, communicating to health care providers and may include required activities or clinical interventions before the drug can be prescribed, dispensed or received.

When is a REMS Necessary?

Consideration of the following factors:

- Seriousness of the known or potential adverse events
- Expected benefit of the drug
- Seriousness of the disease
- Whether the drug is new [i.e., a new molecular entity (NME)]
- Expected duration of treatment
- Size of the population likely to use the drug



REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry

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April 2019
Drug Safety

When is a REMS Necessary?

FDA may require a REMS:

Pre-Approval

FDA determines a REMS is necessary to ensure the benefits of the drug outweigh the risk(s)

Post Approval

FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risk(s)

Elements of a REMS

REMS elements include one or more of the following:

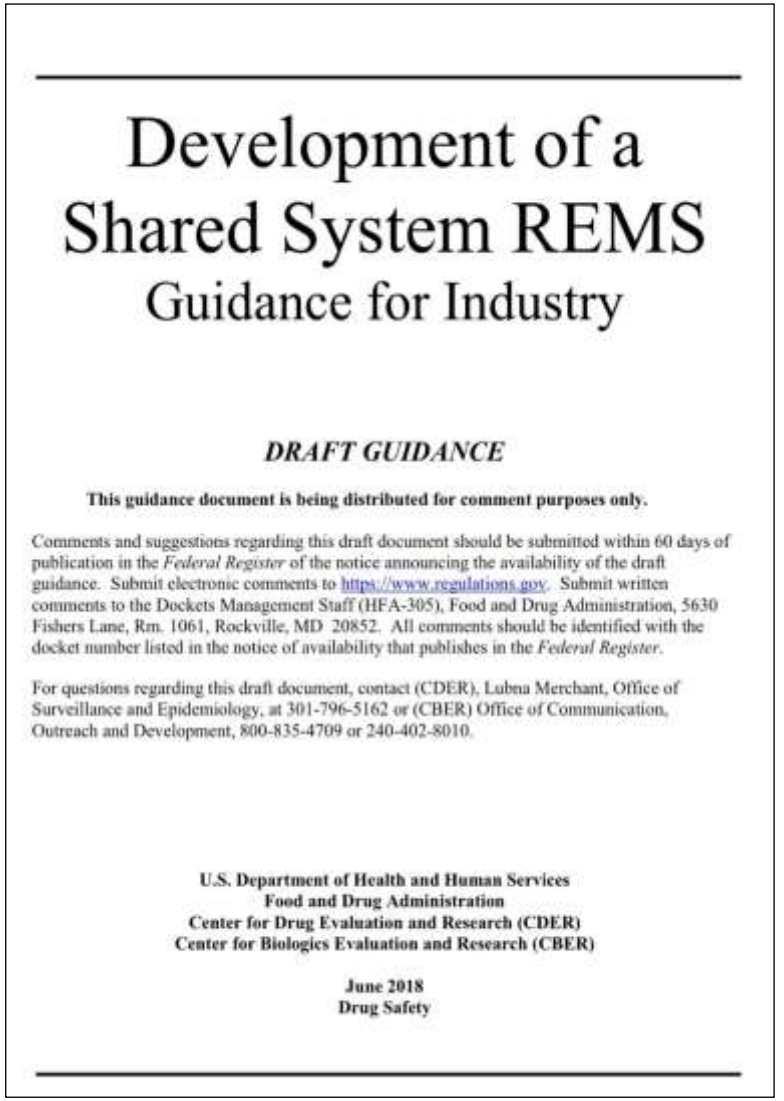
- Communication Plan (not required for ANDAs)
- Medication Guide
- Elements to Assure Safe Use (ETASU)
- Implementation System

All REMS require a timetable for the submission of assessments.

REMS Requirements for ANDAs

If the Reference Listed Drug (RLD) has a REMS, then all ANDAs must also have a REMS using one of the following options:

- Join an already existing Shared System REMS
- Work with the RLD to develop a new Single, Shared System REMS
- Pursue a *separate*, comparable system from the Shared System REMS and work *independently* from the RLD
- Medication Guide only REMS



Development of a Shared System REMS

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft 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 https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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 draft document, contact (CDER), Lubna Merchant, Office of Surveillance and Epidemiology, at 301-796-5162 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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June 2018
Drug Safety

REMS Submissions

Options for submitting a REMS for review:

1. Full REMS proposal
   - No DMF

2. Drug Master File
   - Applicant should submit a cross-reference cover letter and Letter of Authorization (LOA)

REMS Submissions: Full REMS Proposal

Proposed REMS submission includes:

1. REMS (REMS document and REMS materials)
2. REMS Supporting Document

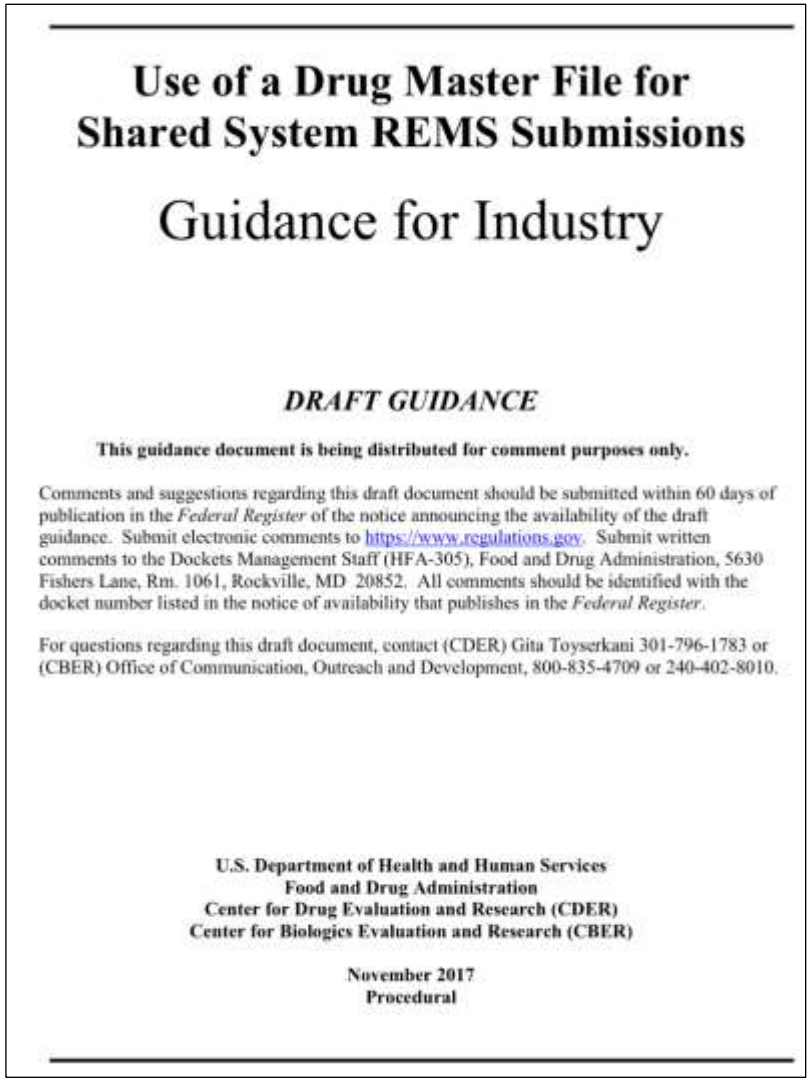
Submission Instructions for each Applicant (No REMS DMF):

- Initial submission (REMS Proposal) - **"PROPOSED REMS for ANDA ######"**
- Subsequent submissions (REMS Amendment) - **"PROPOSED REMS for ANDA ###### - AMENDMENT"**
- REMS document submitted in Structured Product Labeling (SPL) format

REMS Submissions: Drug Master File (DMF)

DMF Submission

- Type V DMF for Shared System (SS) submissions
- Requires a Letter of Authorization (LOA) to be submitted to DMF; DMF holder should send copy to applicant
- Does not need to submit a full REMS proposal



Use of a Drug Master File for Shared System REMS Submissions

Guidance for Industry

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November 2017
Procedural

REMS: Other Things to Know

- A REMS Pre-Approval Notification Letter (RNL) is sent to applicant after the application is accepted for review. Lists the single point of contact to initiate joining the SS REMS

- A REMS proposal is not required at initial ANDA filing, but a statement of intent regarding the REMS is recommended

- If resubmitting after a Complete Response action, the REMS proposal should be part of the resubmission

Challenge Question #1

The RLD in your application has a Shared System REMS, and the REMS does not have an established Type V DMF. What should you submit to your application?

A. Nothing; no submission is necessary.

B. A cover letter cross-referencing the REMS DMF and a Letter of Authorization (LOA) from the DMF Holder, authorizing you to reference the DMF.

C. A full REMS proposal (REMS documents and REMS materials) and REMS Supporting Document.

D. Both B and C.

Challenge Question #2

The RLD in your application has a REMS, and the REMS has an established Type V DMF. What should you submit to your application?

A. Nothing; no submission is necessary.

B. A cover letter cross-referencing the REMS DMF and a Letter of Authorization (LOA) from the DMF Holder, authorizing you to reference the DMF.

C. A full REMS proposal (REMS documents and REMS materials) and REMS Supporting Document.

D. Both B and C.

Challenge Question #3

From Question 2: The RLD in your application has a REMS, and the REMS has an established Type V DMF.

Who else should submit the LOA to their application to meet the REMS requirements?

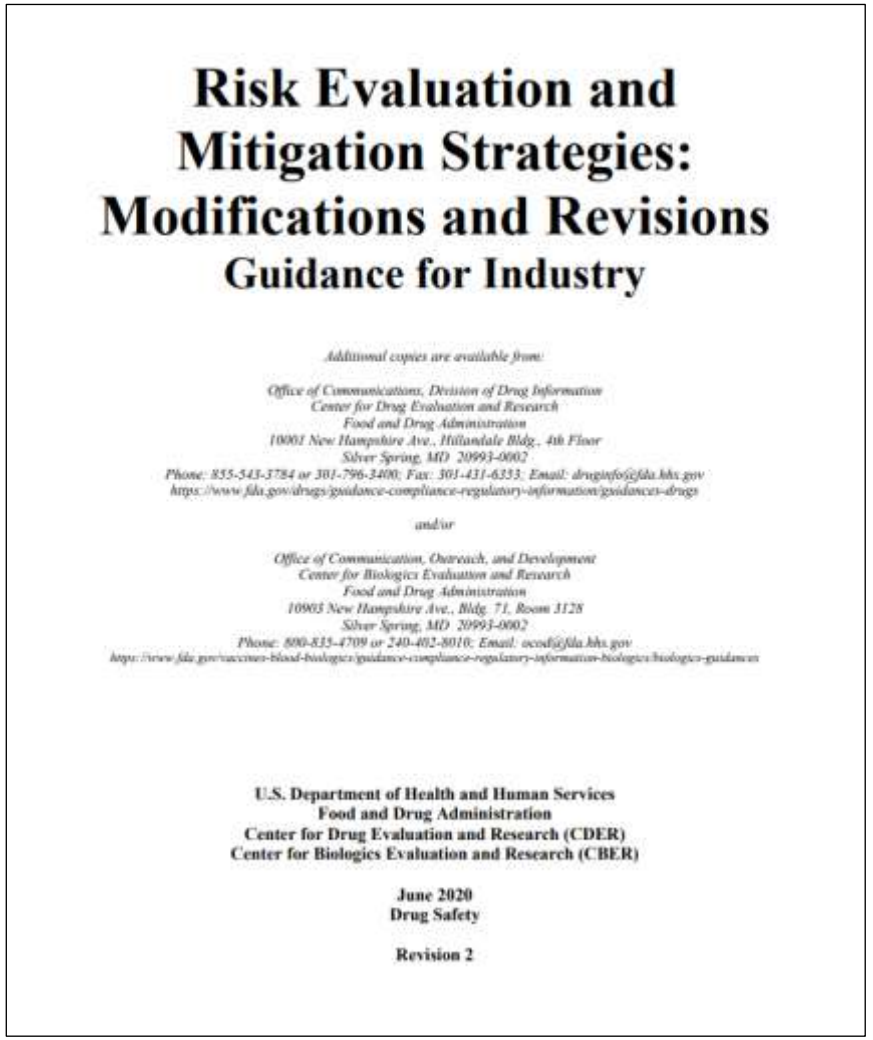
REMS Requirements: Post-Approval

REMS Assessments

- Required for all approved REMS
- Typically, not required for ANDAs that are part of a shared system REMS with an RLD, but can be required if necessary
- Provided in the REMS supporting document

Proposed Changes to REMS

- Application holders (SS REMS Group) can propose changes to an approved REMS at any time
- FDA can require a REMS modification



Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Guidance for Industry

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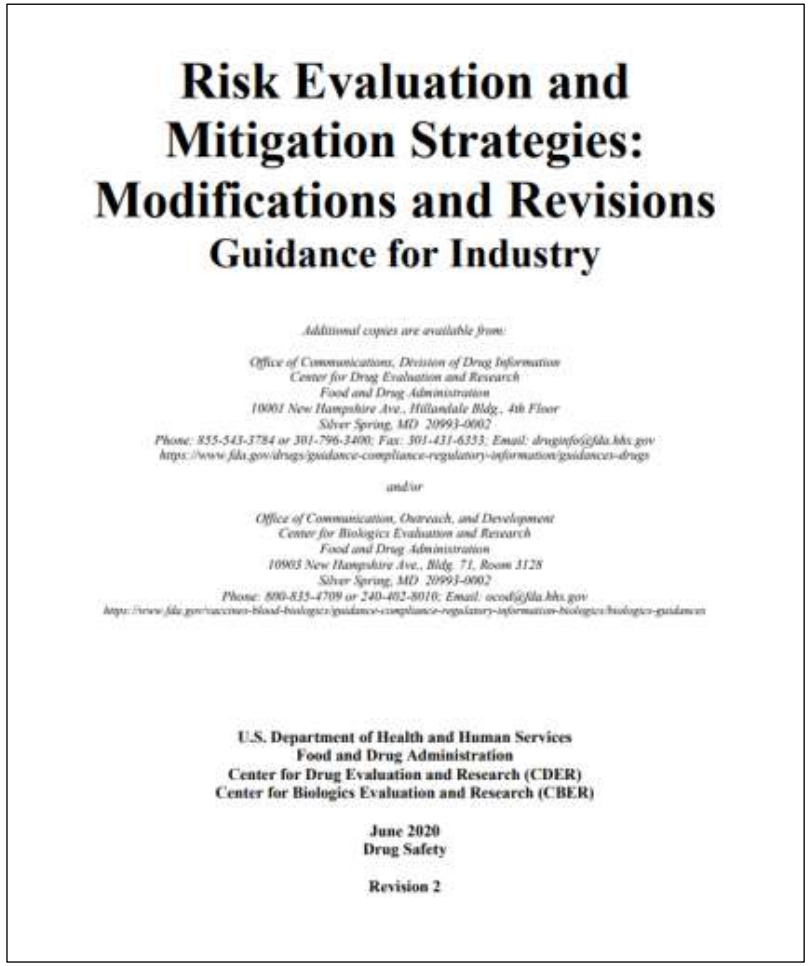
June 2020
Drug Safety

Revision 2

Proposed Changes to REMS

- REMS Revision
- Minor Modification(s)
- Major Modification(s)



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June 2020
Drug Safety

Revision 2

REMS Revision

- Submitted as a REMS Revision (not a supplement)
- Does not require FDA approval
- Can be implemented upon submission
- Examples include:
  - Changes to the application holder name, address, or contact information
  - Editorial changes, grammar, formatting, or typographical errors

Minor REMS Modification

- Submitted as a Changes-Being-Effected (CBE)-30 supplement
- Agency will review and act on proposed minor REMS modifications within 60 days
- Examples include:
  - Addition or removal of a strength or dosage of the drug

Major REMS Modification

- Submitted as a Prior Approval Supplement (PAS)
- FDA will review and act on proposed major REMS modifications within 180 days of receipt
- Requires FDA approval before implementation
- Examples include:
  - Addition, removal, or change to a REMS goal
  - Addition of new information regarding the serious risks associated with the drug

REMS Modification with a DMF

- Approved ANDAs should submit a cross-reference submission as soon as possible (after the modification is submitted to the DMF)

- Approved ANDAs will receive a REMS Modification decision letter after the review of the modification is complete

REMS Modifications: Other Things to Know

- Modifications only apply to drug products with final approval. Pending and Tentatively Approved ANDAs are not required to submit (and will be requested to withdraw the submission)

- Approved ANDAs may receive a REMS Modification Notification letter

Challenge Question #4

Your application, which requires a REMS, is pending review, and the shared system REMS which uses a Type V DMF requires a minor modification. What should you submit to your application regarding the modification?

A. Nothing; no submission is necessary.

B. A cover letter cross-referencing the REMS DMF and a Letter of Authorization (LOA) from the DMF Holder, authorizing you to reference the DMF.

C. A full REMS proposal (REMS documents and REMS materials) and REMS Supporting Document.

D. Both B and C.

Challenge Question #5

You have an approved ANDA and participate in the shared system REMS. The REMS uses a DMF and requires a major modification. What should you submit to your application regarding the modification?

A. Nothing; no submission is necessary.

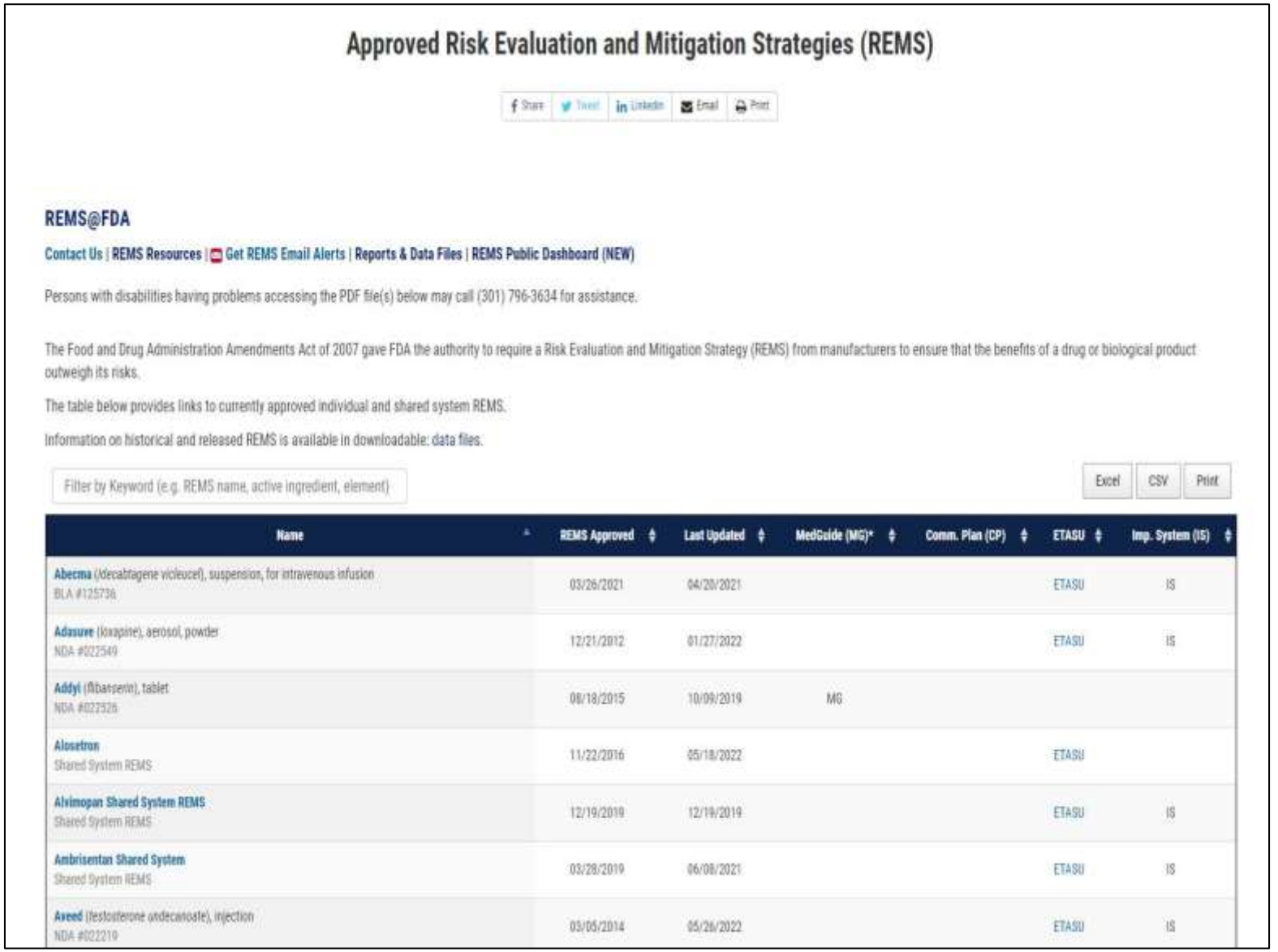
B. A cover letter cross-referencing the major modification to the REMS DMF.

C. A full REMS proposal (REMS documents and REMS materials) and REMS Supporting Document.

D. A cover letter cross-referencing the REMS DMF and a Letter of Authorization (LOA) from the DMF Holder, authorizing you to reference the DMF.

REMS: Helpful Tools

REMS@FDA



Approved Risk Evaluation and Mitigation Strategies (REMS)

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The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

The table below provides links to currently approved individual and shared system REMS.

Information on historical and released REMS is available in downloadable: data files.

Filter by Keyword (e.g. REMS name, active ingredient, element)

Excel | CSV | Print

Name	REMS Approved	Last Updated	MedGuide (MG)*	Comm. Plan (CP)	ETASU	Imp. System (IS)
Abecma (idecabtagene vicleucel), suspension, for intravenous infusion BLA #125736	03/26/2021	04/20/2021			ETASU	IS
Adasuve (loxapine), aerosol, powder NDA #022549	12/21/2012	01/27/2022			ETASU	IS
Addyi (flibanserin), tablet NDA #022526	08/18/2015	10/09/2019	MG			
Alosetron Shared System REMS	11/22/2016	05/18/2022			ETASU	
Alvimopan Shared System REMS Shared System REMS	12/19/2019	12/19/2019			ETASU	IS
Ambrisentan Shared System Shared System REMS	03/28/2019	06/08/2021			ETASU	IS
Aveed (testosterone undecanoate), injection NDA #022219	03/05/2014	05/26/2022			ETASU	IS

REMS: Helpful Tools

FDA REMS Public Dashboard

Resources

Guidance Documents

Search for FDA Guidance Documents

- *REMS: FDA's Application of Statutory Factors in Determining When a REMS is Necessary for Industry*
- *Development of a Shared System REMS Guidance for Industry (Draft Guidance)*
- *Format and Content of a REMS Document Guidance for Industry*
- *Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry*
- *Use of a Drug Master File for Shared System REMS Submissions Guidance for Industry (Draft Guidance)*

Additional REMS Information

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REMS Public Dashboard