Risk Evaluation and Mitigation Strategies (REMS) for Generic Drugs: Best Practices for Proposed REMS Submissions

CAPT Stacy Barley, REMS Team Lead

Division of Clinical Safety and Surveillance
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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Learning Objectives

What is a REMS?

- Define a REMS and REMS requirements

Types of REMS Submissions

- Describe development of Shared System (SS) REMS with a Drug Master File (DMF) vs. without a DMF, and
- Separate Comparable REMS

Effective Communication

- Communicate with FDA regarding the status of your REMS
- Communicate with the applicable reference listed drug holder regarding a shared system REMS

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).

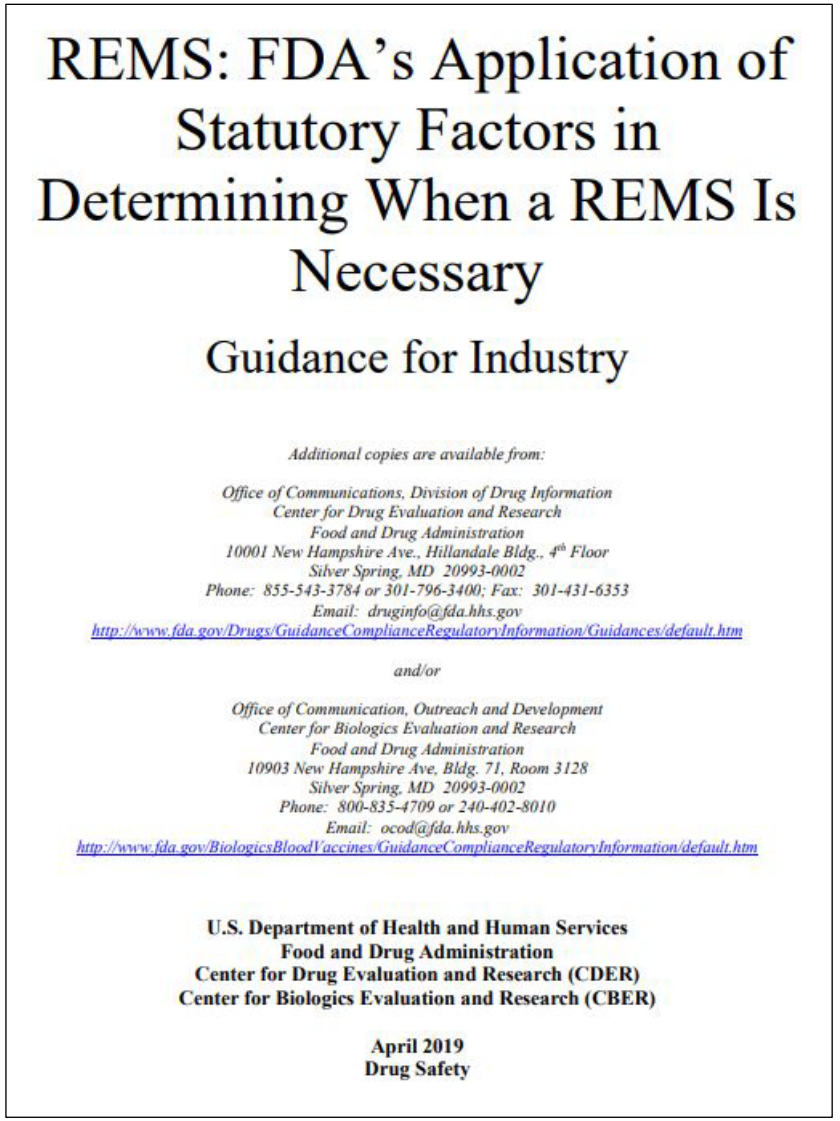
2. Develop a risk management plan beyond the labeling to ensure the benefits of a drug outweigh known risks.

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

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave, Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

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 2019
Drug Safety

REMS Submission Requirement

FDA may require a REMS:

Pre-Approval

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

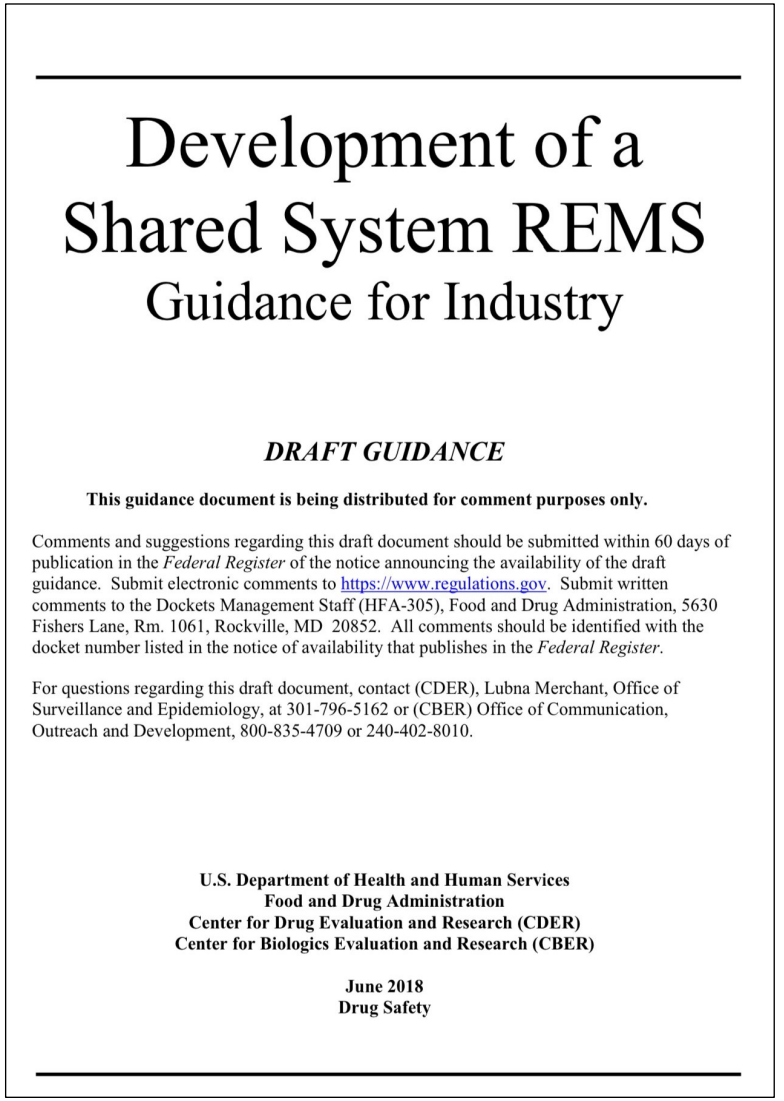
Post-Approval

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)

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:

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



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)
Center for Biologics Evaluation and Research (CBER)

June 2018
Drug Safety

REMS: Important Reminders

- Know your product! Access the REMS@FDA website to determine if the RLD or Reference Standard (RS) has a REMS
- Search for and review the latest REMS guidances in advance of your submission (see Resources Slide)
- A REMS Pre-Approval Notification Letter (RNL) is sent to the applicant **after** the application is accepted for review
- 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

What to Submit

Submit a full REMS proposal:

- If there is no Type V DMF
- If you do not plan to work with the RLD
- Submission of REMS proposal must be very detailed (noted on next slide)

Using Type V DMF REMS:

- Best option!!
- Only need to submit a cover letter and letter of authorization (LOA) to ANDA file (no full REMS proposal needed)
- LOA must also be in the DMF

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

Communication is Key to Success

Communicating with the FDA

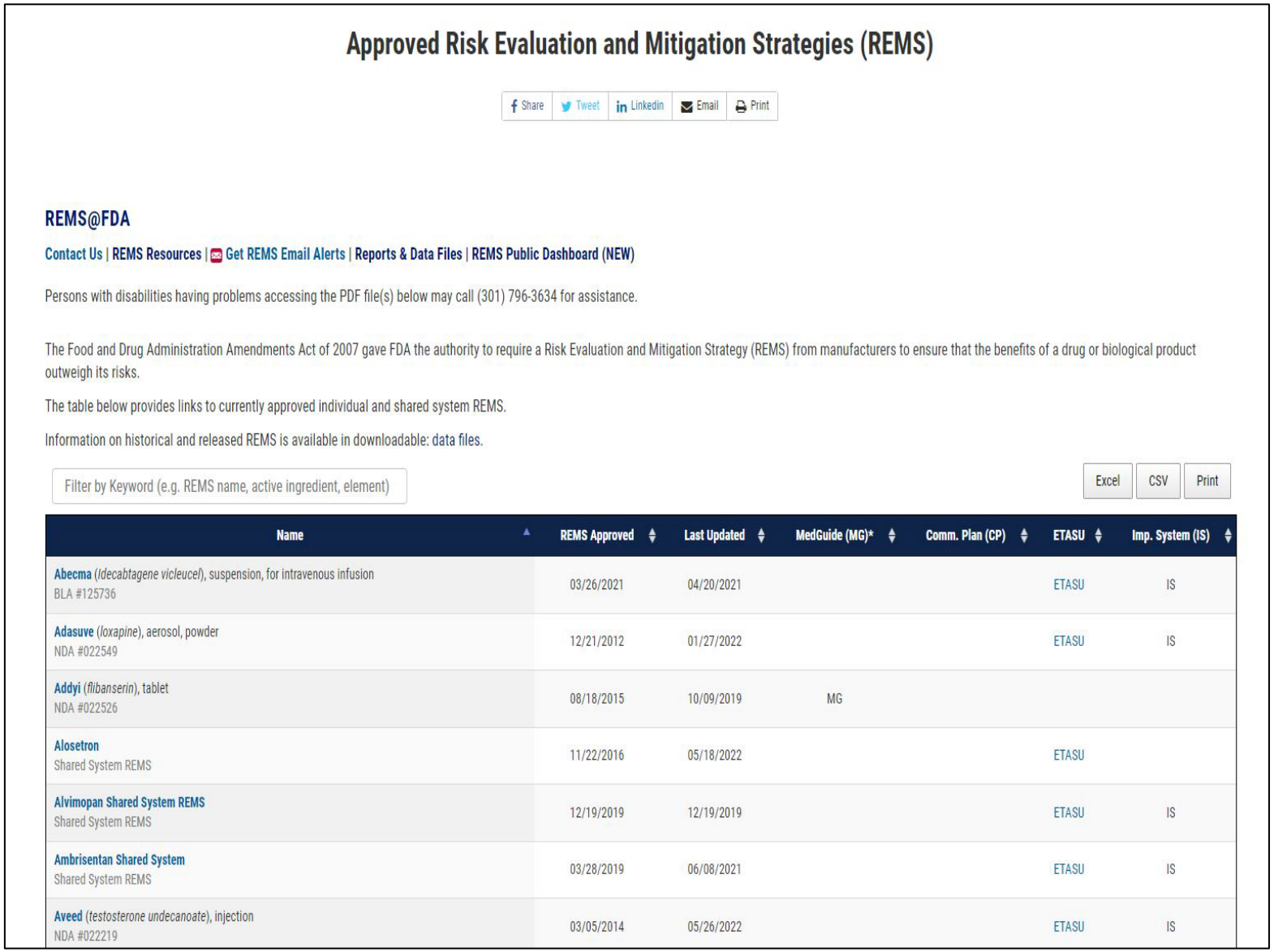
- Review your Pre-Approval REMS Notification Letter (RNL)
- Submit disclosure Authorization letter (if applicable)
- Attend Kick-off Meeting scheduled by FDA for RLD, and generic drug applicant(s)
- Submit biweekly updates
- Contact the REMS Coordinator listed in your Pre-Approval RNL if you need help

Communicating with the RLD

- Reach out to the RLD as soon as you receive your Pre-Approval RNL
- Collaborate early to develop a Shared System REMS or obtain a LOA to a REMS DMF
- Review the FDA REMS website frequently throughout your review to ensure there are no REMS updates to the RLD or existing SS REMS

REMS: Helpful Tools

REMS@FDA



Approved Risk Evaluation and Mitigation Strategies (REMS)

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REMS@FDA

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Persons with disabilities having problems accessing the PDF file(s) below may call (301) 796-3634 for assistance.

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

REMS@FDA

REMS Public Dashboard