Risk Evaluation and Mitigation Strategies (REMS) for Generic Drugs

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Objectives

- Provide background information on REMS and identify the REMS requirements for ANDAs
- Describe the ANDA submission process for REMS/Elements to Assure Safe Use (ETASU) products
- Discuss the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act and its implications for ANDAs

What is a REMS?

The Food and Drug Administration Amendments Act (FDAAA) of 2007 provided a new safety authority under Section 901 that required applicants to:

- Develop and comply with REMS (505-1) of the Federal Food, Drug and Cosmetic Act (FD&C Act)
- Develop a required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks

REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary, April 2019: https://www.fda.gov/media/100307/download

Examples of the Types of Risks REMS Requirements Aim to Mitigate

Risk Example	Possible REMS Action
Serious infection	Patient education on initial warning signs prior to prescribing
Severe allergic reaction	Healthcare professional must be certified prior to administration of the product
Liver damage	Liver function monitoring while patient is taking the drug
Severe birth defects	Negative pregnancy test prior to dispensing each prescription

When FDA Can Require a REMS?

- **Before approval** if FDA determines a REMS is necessary to ensure the benefits of the drug outweigh the risks
- **Post-approval** if FDA becomes aware of *new safety information* and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks

Possible Components of a REMS

A REMS can include one or more of the following:

- Medication Guide or Patient Package Insert
- Communication Plan for Healthcare Providers
  - Not required for ANDAs
- Implementation System
- Elements to Assure Safe Use (ETASU)

Implementation System

- REMS may include an implementation system related to the following ETASU:
  - Certification of pharmacies and hospitals
  - Healthcare settings
  - Safe use conditions
- May require the sponsor to take reasonable steps to:
  - Monitor and evaluate implementation of such elements by healthcare professionals; and
  - Work to improve implementation of such elements by such persons

Elements to Assure Safe Use (ETASU)

A REMS may require any or all of the following:

- Certification or specialized training of Healthcare Providers who prescribe the drug
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug in limited settings, e.g., hospitals
- Dispensing/administration of drug only with evidence of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Enrollment of treated patients in registries

Example of REMS with ETASU

Sabril (vigabatrin)

- For the treatment of epilepsy and infantile spasms
- Risk of new and worsening vision loss, including permanent vision loss
- ETASU:
  - Prescriber certification
  - Pharmacy certification
  - Patient enrollment
  - Periodic vision assessment
  - Assessment of patient's response to Sabril

Example of REMS with ETASU

Letairis (ambrisentan)

- For the treatment of pulmonary arterial hypertension (PAH)
- Risk of birth defects
- ETASU:
  - Provider certification
  - Pharmacy certification
  - Patient enrollment and monitoring

FDAAA REMS Requirement for ANDAs

If the referenced listed drug (RLD) has a REMS, then all ANDAs must also have a REMS in one of the following pathways:

- Join an already existing Shared System (SS) REMS with ETASU
- Work with the RLD to develop a new Single, Shared System (SSS) REMS with ETASU
- Pursue a separate, comparable system from the Shared System ETASU REMS and work independently from the RLD
- Medication Guide **only** REMS: does not require the ANDA to interact with the RLD

See the draft Shared System REMS Guidance at: https://www.fda.gov/media/113869/download

Separate REMS for ANDAs

- Same goals
- Same ETASU
  - Must achieve same level of safety
  - How the elements are operationalized may differ
  - Applicants should explain and justify any differences in operations

Separate REMS for ANDAs

Things to consider in developing a separate REMS program:

- Will the operational differences shift burden to other stakeholders?
- Will the operational differences cause confusion for stakeholders?
- Will the operations allow for other ANDAs to join the program?

The CREATES Act

The Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act was passed in December 2019

- Provides a new pathway for developers of drug and biological products to obtain samples of brand products
- Facilitates the timely entry of lower-cost generic and biosimilar versions of those drugs and biological products

The CREATES Act *(cont)*

The CREATES Act:

- *Removes* the requirement under Section 505-1(i) of the FD&C Act that states that an ANDA product and its reference listed drug shall use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.
- Allows the ANDA applicant to develop a proposed REMS that uses a different, comparable aspect of the ETASU.
  - An adequate rationale to support any deviations from the RLD REMS should be provided.

- The Pomalidomide REMS Program is an example of a separate REMS program approved under the CREATES Act.

ANDA Submission Process

- A REMS submission is not required at the time of initial ANDA filing, but a statement of intent regarding the REMS pathway is recommended.

- The Office of Generic Drugs notifies each ANDA applicant of the REMS requirement by sending a REMS Notification Letter (RNL).
  - The RNL outlines the REMS requirements for the applicable listed drug and provides instructions on joining an established shared system REMS or developing a separate, comparable system.

Post Approval REMS Requirements

Assessments

- Every REMS for a New Drug Application (NDA) or Biologics License Application (BLA) product must have a timetable for submission of assessments of the REMS (505-1(d))
- REMS can require additional assessments
- Can be eliminated after 3 years

These are only requested of ANDAs in a separate shared system consisting of ANDAs only

Post Approval REMS Requirements *(cont)*

Modifications

- Sponsors of an approved SS REMS and a NDA sponsor of an approved REMS may submit REMS modification proposing addition, modification, or removal of any goal or element
  - Must include adequate rationale for proposal
- FDA must review/act on REMS modifications within timeframes specified in Guidance

Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry, June 2020: https://www.fda.gov/media/128651/download

Post Approval REMS Requirements *(cont)*

After a REMS is approved, FDA may require submission of a proposed modification if FDA determines that one or more goals or elements should be added, modified, or removed from the REMS to:

- Ensure the benefits of the drug outweigh the risks
- Minimize the burden on the health care delivery system of complying with the REMS

Additional Information For Industry

- FDA REMS Website: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

- FDA Guidance Documents
  - Development of a Shared System REMS Guidance for Industry: https://www.fda.gov/media/113869/download; June 2018
  - REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry: https://www.fda.gov/media/100307/download; April 2019
  - Format and Content of a REMS Document Guidance for Industry: https://www.fda.gov/media/77846/download; October 2017
  - Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry: https://www.fda.gov/media/128651/download; June 2020

Challenge Question #1

Which of the following statements about REMS is NOT true?

A. If the RLD has a REMS, then all ANDAs must also have a REMS.

B. A REMS is required before approval if FDA determines it is necessary to ensure the benefits of the drug outweigh the risks.

C. A REMS is required post-approval if FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks.

D. Every ANDA must have a timetable for submission of assessments of the REMS.

Challenge Question #2

What are the possible components of a REMS for an ANDA?

A. Medication Guide or Patient Package Insert
B. Communication Plan for Healthcare Providers
C. Implementation System
D. Elements to Assure Safe Use (ETASU)
E. A, C, and D

Conclusion

- REMS are a valuable tool for patient safety
- They can employ a variety of strategies to ensure benefits of a drug outweigh risks
- They are specifically tailored to a particular drug and particular risk
- REMS programs are often shared by multiple application holders (e.g., ANDAs and NDA)

Thank You!

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