Recent Changes to REMS Statute and Development of Shared System REMS

Elaine Lippmann, J.D.
Senior Regulatory Counsel
Office of Regulatory Policy

Laura Zendel, Pharm.D. BCPS
Team Leader
Division of Risk Management

CDER | US FDA

Pharmacovigilance and Risk Management Conference
June 9, 2020

Learning Objectives

- Examine the changes to the REMS statute through the Appropriations Act of 2020
- Understand implications for ANDA review/approval
- Learn about FDA's approach to shared REMS following these changes
- Describe considerations during the development of Shared System REMS

Background

REMS and Generics

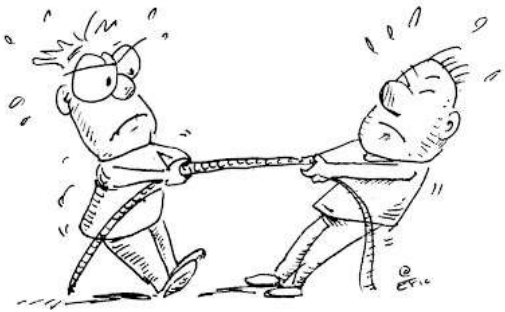
- Generic product (ANDA) referencing a drug with a REMS is subject to these components of the REMS:
  - Med Guide or patient package insert (PPI)
  - Elements to Assure Safe Use (ETASU)
- Original statute required that generic use a "**single, shared system**" with innovator for any ETASU

Benefits of a single shared system

- Reduces burden for different stakeholders
  - single portal to access materials and other documentation and information about the program
  - prescribers, pharmacies, and healthcare settings complete certification and other administrative requirements once rather than for each individual drug
- Potential for cost sharing among all sponsors

Burdens of Forming a Shared System

- Negotiations and establishment of agreements may involve numerous complex issues (e.g., voting rights, cost sharing, product liability)
- Challenges of transitioning REMS to a multi-source environment
- Parties are marketplace competitors, and sometimes adversaries in patent litigation related to the drug product
- Can involve a large number of companies
- Uncertainties in ANDA approval/pressures of GDUFA timelines



Appropriations Act of 2020

Changes to Sec. 505-1

Removal of Single, Shared System Requirement

Before

For ETASU, ANDA shall use a SSS with innovator. FDA can waive that requirement if:

1. The burdens of forming SSS outweigh benefits; **or**
2. ANDA unable to obtain license to REMS patents.

After

For ETASU, ANDA may use –

1. A single, shared system with the listed drug; **or**
2. A different, comparable aspect of the ETASU.

Sec. 505-1(i)(1)(C)(i)

SSS Requirement in Some Cases

- FDA can still require use of a SSS if it "determines that no different, comparable aspect of the [ETASU] could satisfy the requirements." Sec. 505-1(i)(1)(C)(ii)

- Now the default is that generics have an option, but FDA can affirmatively decide a SSS is necessary.

Shared REMS for Subsequent Generics

- If FDA approves a separate REMS for an ANDA, it can require that the separate REMS "can be used with respect to any other drug that is the subject of an application under section 505(j) or 505(b) that references the same listed drug." Sec. 505-1(i)(3)

- This provision is to avoid the proliferation of multiple REMS for the same drug.

Definition of Separate REMS

"Different, comparable aspect of the ETASU" means:

- Uses different methods or operational means than the REMS for the listed drug; but
- Achieves the same level of safety.

Sec. 505-1(m)

REMS Modifications

Before

FDA can require a REMS Modification if it determines it necessary to:

1. Ensure the benefits of the drug outweigh the risks; or
2. Minimize the burden on the healthcare delivery system.

After

FDA can require a REMS Modification if it determines it necessary to:

1. Ensure the benefits of the drug outweigh the risks;
2. Minimize the burden on the healthcare delivery system; **or**
3. **Accommodate different, comparable aspects of the elements to assure safe use for a drug that is subject to an application under section 505(j), and the applicable listed drug.**

Sec. 505-1(g)(4)(B)

Implications of Changes

ANDAs Have Two Pathways

- Generics have a clear path to approval without depending on cooperation from innovator.
- Submit either a SSS REMS or separate REMS as part of your application.

Separate Comparable REMS

- No need for waiver, but FDA must determine that separate REMS is “comparable” to the existing REMS.
- FDA can determine that no separate REMS could fulfill the requirements.

FDA Approach to Shared Systems

Following the Changes

Encouraging Development of Shared REMS

Shared systems are still ideal in most circumstances.

Priority for FDA – actively facilitate voluntary development of shared systems

FDA Actions

- Reopened comment period on *Draft Guidance: Development of Shared System REMS*
- Held series of listening sessions with brand and generic companies
- Synthesizing feedback to help improve process
- Collecting/formulating best practices

Challenge Question #1

If an ANDA applicant submits a proposal for a separate REMS, FDA will:

A. Determine whether it should grant a waiver

B. Make sure the separate REMS is not used by other companies

C. Determine whether it is comparable to the innovator REMS

D. Make sure it functions exactly the same as the innovator REMS

Challenge Question #2

Which of the following statements is NOT true?

A. FDA will not engage with sponsors about their REMS until approval.

B. Shared system REMS usually improve efficiencies for stakeholders

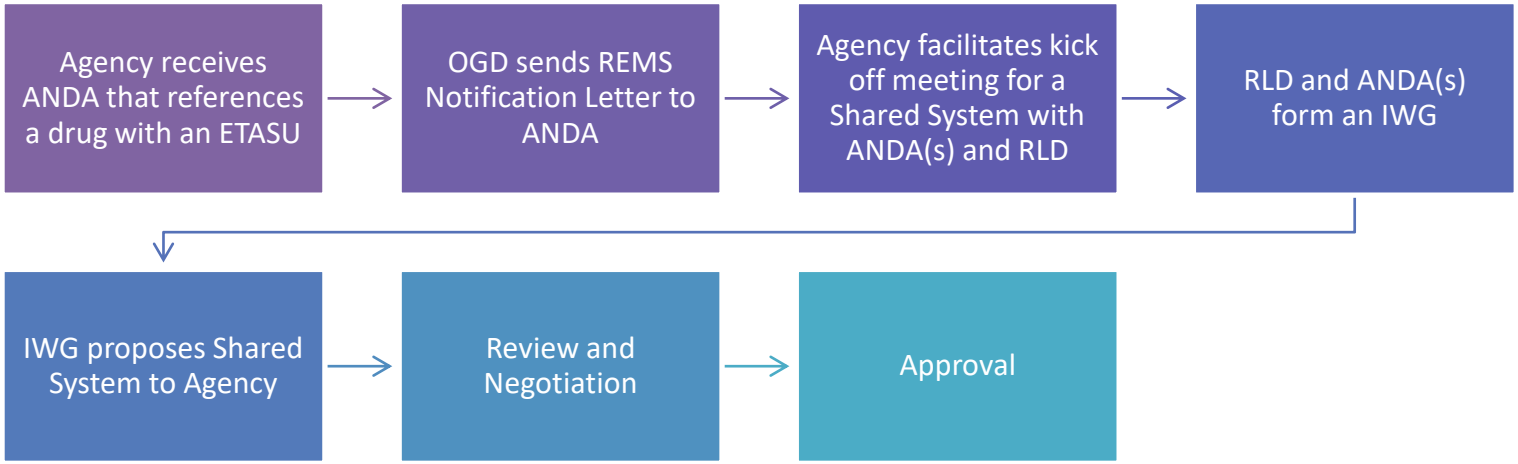
C. FDA can require a REMS modification to accommodate a separate system

D. FDA can require use of a single shared system if a separate one will not meet necessary requirements

Laura Zendel, Pharm.D. BCPS

Development of Shared System REMS

Steps in the Formation of a Shared REMS



Industry Working Groups (IWG)

Facilitates negotiations and agreements between the Applicants

Confidentiality	Governance	Voting structure	Cost sharing	Drug distribution	Third party vendors

Establishes a single point of contact for communications with the FDA

All REMS proposals and communications must be submitted to each application separately.

COORDINATION IS KEY

ADDITIONAL ASSISTANCE IS AVAILABLE VIA EMAIL AND TELECONFERENCE

A Type V DMF simplifies SS REMS submission and review.

Changes to the SS REMS are OK as long as it achieves the same level of safety.

Operational Changes

Transition activities from Pharmacy to REMS Coordinating Center

Expanding to retail setting

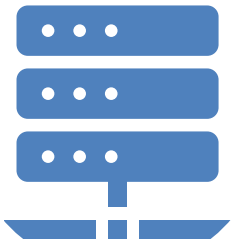
Additional Functions

Online Enrollment

Expanding website or portal

Reduce burden and confusion associated with a Separate REMS.

Establish communication between the separate REMS and the Established REMS



Shared Database

Open Communication

Have a Transition Plan.

How will you transition between programs?

Automatic enrollment vs. re-enrollment for stakeholders

Stakeholder Outreach

Timeline

Approval Challenges

APPROVAL OF A NEW SS REMS AND A MODIFICATION OF THE RLD REMS

STATUS OF ANDAS FLUCTUATES

The RLD holder submits a bifurcated REMS to account for Tentative Approvals.

Bifurcated REMS Document

Part A: the current REMS that applies only to the RLD and is operational before approval of the first ANDA

Part B: the Shared System REMS that becomes operational upon full approval of the first ANDA

Challenge Question #3

Which of the following statements is NOT true?

A. The IWG establishes a single point of contact for communication with the FDA.

B. Single, Shared System REMS proposals only need to be submitted to the NDA.

C. Changes to the operations of the SS REMS are OK if it achieves the same level of safety.

D. A transition plan should be included with the proposed SSS REMS.

Challenge Question #4

A Bifurcated REMS accounts for:

A. Creation of a separate REMS

B. Changes in operations of a SSS REMS

C. Full Approval of an ANDA

D. Tentative Approval of an ANDA

Summary

- Generics can submit either a SSS REMS or a Separate REMS.
- Changes are OK if it achieves the same level of safety.
- SSS are ideal in most circumstances.

Resources

- General REMS info
- REMS@FDA (info about specific REMS programs)
- Draft Guidance: Development of Shared System REMS
- Draft Guidance: Use of a DMF for Shared System REMS

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Elaine Lippmann, J.D.
Senior Regulatory Counsel
Office of Regulatory Policy

Laura Zendel, Pharm.D. BCPS
Team Leader
Division of Risk Management

CDER | US FDA

Pharmacovigilance and Risk Management Conference
June 9, 2020


FDA
U.S. FOOD & DRUG
ADMINISTRATION