

# Risk Evaluation and Mitigation Strategies (REMS)

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# Agenda

1. Overview of REMS
  - a) Purpose
  - b) Legal authority
  - c) Tools they employ
2. REMS Assessments and Modifications
3. REMS Requirements for Generics
  - a) The single, shared system requirement
  - b) Waivers of the single, shared system requirement

# What is a REMS?

- Risk Evaluation and Mitigation Strategy
- Authority given by the FDA Amendments Act (FDAAA) in 2007 (Section 505-1 of the FD&C Act)
- A required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks.





# Examples of the Types of Risk 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 administer 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

## REMS: Key Points

- Drug sponsors develop REMS programs, FDA reviews and approves them
- REMS programs can be designed for a single drug or a class of drugs
- Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs

## Possible Components of a REMS

A REMS can include one or more of the following:

- Medication Guide (MG) or Patient Package Insert
- Communication Plan (CP) for Healthcare Providers
- Elements to Assure Safe Use (ETASU)
- Implementation System

# Medication Guide

- Provides FDA-approved *patient-friendly* labeling
- Must meet requirements of 21 CFR 208: MG can be required if FDA determines one or more:
  - Patient labeling could help prevent serious adverse events
  - The product has serious risks that could affect patient’s decision to use or continue to use
  - Patient adherence to directions is crucial to product effectiveness





<b>Medication Guide</b> <b>TRADENAME<sup>®</sup></b> <i>[Insert phonetic spelling]</i> (chemical name) <i>[Insert dosage form]</i> , CII
<b>TRADENAME is:</b> <ul style="list-style-type: none"><li>• A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.</li><li>• A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.</li><li>• Not for use to treat pain that is not around-the-clock.</li></ul>
<b>Important information about TRADENAME:</b> <ul style="list-style-type: none"><li>• Get emergency help right away if you take too much TRADENAME (overdose). When you first start taking TRADENAME, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.</li><li>• Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.</li></ul>
<b>Do not take TRADENAME if you have:</b> <ul style="list-style-type: none"><li>• severe asthma, trouble breathing, or other lung problems.</li><li>• a bowel blockage or have narrowing of the stomach or intestines.</li></ul>
<b>Before taking TRADENAME, tell your healthcare provider if you have a history of:</b> <ul style="list-style-type: none"><li>• head injury, seizures</li><li>• liver, kidney, thyroid problems</li><li>• problems urinating</li><li>• pancreas or gallbladder problems</li><li>• abuse of street or prescription drugs, alcohol addiction, or mental health problems.</li></ul> <b>Tell your healthcare provider if you are:</b> <ul style="list-style-type: none"><li>• pregnant or planning to become pregnant. Prolonged use of TRADENAME during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.</li><li>• breastfeeding. TRADENAME passes into breast milk and may harm your baby.</li><li>• taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking TRADENAME with certain other medicines can cause serious side effects that could lead to death.</li></ul>
<b>When taking TRADENAME:</b> <ul style="list-style-type: none"><li>• Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.</li><li>• Take your prescribed dose <i>[insert frequency, e.g., every X hours at the same time every day]</i>. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.</li><li>• Swallow TRADENAME whole. Do not cut, break, chew, crush, dissolve, snort, or inject TRADENAME because this may cause you to overdose and die.</li><li>• Call your healthcare provider if the dose you are taking does not control your pain.</li><li>• Do not stop taking TRADENAME without talking to your healthcare provider.</li><li>• After you stop taking TRADENAME, flush any unused <i>[insert dosage form]</i> down the toilet.</li></ul>
<b>While taking TRADENAME DO NOT:</b> <ul style="list-style-type: none"><li>• Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.</li><li>• Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with TRADENAME may cause you to overdose and die.</li></ul>
<b>The possible side effects of TRADENAME:</b> <ul style="list-style-type: none"><li>• constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.</li></ul> <b>Get emergency medical help if you have:</b> <ul style="list-style-type: none"><li>• trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.</li></ul> <p>These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to <a href="http://dailymed.nlm.nih.gov">dailymed.nlm.nih.gov</a></p> <p>Manufactured by: <i>[insert name and address]</i> and/or Distributed by: <i>[insert name and address]</i>, <a href="http://www.TRADENAME.com">www.TRADENAME.com</a> or call 1-800-XXX-XXXX</p>
<b>This Medication Guide has been approved by the U.S. Food and Drug Administration.</b>

[Click here to see the PDF template online](#)

## Examples of REMS with Med Guide

- Xarelto (rivaroxaban)
  - MG, CP, timetable
    - Goal: To inform nonvalvular atrial fibrillation **patients** that XARELTO should not be stopped without first informing their healthcare professional so as to minimize the risks of post-discontinuation thrombotic events.
- AndroGel (testosterone gel)
  - MG and timetable
    - Goal: To inform **patients** about the serious risks associated with the use of AndroGel

# Communication Plan

- FDA-approved materials used to aid sponsor's implementation of REMS and/or inform healthcare providers about risks
  - Cannot be directed to patients
- Communication plan may include:
  - “Dear Healthcare Professional” letters
  - Dissemination of information to HCPs through professional societies
  - Information about the REMS to encourage implementation

## Example of Communication Plan

- Arcapta Neohaler (indacaterol maleate)
  - Goals:
    - To inform healthcare providers and prescribers of the increased risk of asthma related death and serious outcomes with the long-acting beta2-adrenergic agonists (LABAs) including ARCAPTA NEOHALER when used to treat asthma.
    - To inform healthcare providers and prescribers of the appropriate use of ARCAPTA NEOHALER, and its approved indication (COPD).

## Elements to Assure Safe Use (ETASU)

ETASU are required medical interventions or other actions by healthcare professionals prior to prescribing or dispensing the drug. Some actions may also be required in order for the patient to continue on treatment.

# Elements to Assure Safe Use (ETASU)



Depending on the risk, a REMS may require any or all of the following:

- A. Certification or specialized training of HCPs who prescribe the drug
- B. Certification of pharmacies or other dispensers of the drug
- C. Dispensing/administration of drug in limited settings e.g., hospitals
- D. Dispensing/administration of drug only with evidence of safe-use conditions
- E. Each patient using the drug is subject to certain monitoring
- F. 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



# Implementation Systems

- REMS may include an implementation system related to the following ETASU:
  - Certification of pharmacies and hospitals
  - Healthcare settings
  - Safe use conditions
- May require applicant to take reasonable steps to—
  - Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and
  - Work to improve implementation of such elements by such persons

# Timetable for Submission of Assessments

- Every REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS (505-1(d))
- The timetable for submission of assessments must include an assessment
  - by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved
- REMS can require additional assessments
- Can be eliminated after three years

# REMS Assessments

Must include:

With respect to each REMS goal, an assessment of the extent to which the REMS is meeting the goal or whether one or more goals/elements should be modified

# Information Provided in Assessments: Examples

- Survey data
- Summary of adverse events
- Prescriber compliance
- Use data
- Number and percentages of patients who were monitored for potential serious adverse events during treatment with the drug

# REMS Modification

- Applicant 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 mods within timeframes specified in Guidance

(Risk Evaluation and Mitigation Strategies: Modifications and Revisions, April 2015)

# REMS Modification

- After REMS is approved, FDA may require submission of a proposed modification if FDA determines that 1 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

# REMS requirements for generics (ANDA)

- Where innovator product is subject to REMS, ANDA referencing that product is subject to:
  - Med Guide
  - ETASU
    - ANDA must use a ***single, shared system*** with the innovator for any ETASU (unless FDA waives this requirement, in which case ANDA can use different, but comparable system)

# Single Shared System REMS

- NDA and all ANDAs
- Single REMS document, REMS materials (except MGs), and supporting documents applicable to all drugs
- Shared database and infrastructure



# 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

# SSS Development Process

1. FDA notifies applicant of REMS requirement
2. ANDA applicant contact RLD holder
3. Kick-off meeting
4. Companies form industry working group
5. Agency forms review team
6. FDA facilitates when needed
7. REMS submission

# SSS Development Process

1. The Office of Generic Drugs (OGD) notifies each ANDA sponsor of the requirement for a SSS by sending a REMS notification letter.
  - The REMS notification letter (1) notifies the ANDA sponsor of the requirement of a SSS, and (2) directs the ANDA sponsor to contact the sponsor of the reference listed drug.

## SSS REMS Development Process (Cont'd)

2. ANDA holders make initial contact with RLD holder and initiate discussions about a SSS REMS
3. FDA hosts a “kick-off” meeting to convey expectations and facilitate planning to move SSS REMS development forward

## SSS REMS Development Process (Cont'd)

4. Companies may form an “industry working group” (IWG) to develop a proposal for the shared REMS
  - FDA instructs the IWG sponsors to identify a single point of contact to represent the IWG, and emphasizes the importance of first working out the cost and governance structures
  - IWG provides bi-weekly updates to the Agency
5. The Agency forms a REMS review team including staff from a number of Offices within the Center
  - FDA communicates expected timeframes for milestones
  - FDA schedules periodic teleconferences with the IWG

## SSS REMS Development Process (Cont'd)

6. When a company indicates to the Agency that another company (brand or generic) in the IWG is not receptive or responsive to efforts to develop a SSS REMS, the Agency may serve as facilitator to aid in reaching resolution.
7. Once developed, the SSS REMS proposal is submitted by the innovator and generic companies to the Agency for review.
  - FDA instructs the IWG how to submit the REMS proposal.

## Issues to be Addressed in Negotiations

- Cost-sharing
- Confidentiality
- Product liability concerns
- Anti-trust concerns
- Access to a license for elements protected by patent
- Experience/trust gap(s)

# FDA Perspective on Waiver

- Shared system REMS fulfill Congressional intent to reduce end-user burden and foster ease of access to generic products with REMS.
- The waiver provision provides an alternative path for approval of generic drugs if a single shared system is not feasible.



# Waiver of the SSS Requirement

- Expectation is successful formation of SSS
- If, during the course of negotiations, FDA or the sponsors believe that a waiver may be warranted, FDA will:
  - Determine whether the statutory criteria for a waiver have been met
  - Review a separate proposed REMS submission by the ANDA sponsor(s)

# Criteria for Waiver

The Secretary **may waive the requirement** for a drug that is the subject of an abbreviated new drug application, and permit the applicant to **use a different, comparable aspect** of the elements to assure safe use, if the Secretary determines that—

- (i) the **burden of creating a single, shared system outweighs the benefit**. . . taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product; **or**

# Criteria for Waiver

...(ii) an aspect of the elements to assure safe use for the applicable listed drug is **claimed by a patent** that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the applicant for the abbreviated new drug application certifies that it has **sought a license for use** of an aspect of the elements to assure safe use for the applicable listed drug and that it was **unable to obtain a license**.

## Separate REMS for ANDA(s)

FDA may waive the requirement for a SSS and permit the ANDA to use a “**different, comparable aspect**” of the ETASU (505-1(i)).

# Separate REMS for ANDA(s)

- 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 ANDA(s)

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?

# Waiver Process

- FDA may waive the SSS requirement upon request from a sponsor.
- FDA may determine on its own that waiver is appropriate without receiving a request from a sponsor.
- In each circumstance, FDA conducts an individual analysis based on the statutory criteria for waiving the SSS requirement.

# A Complete REMS Submission

- REMS
- REMS Supporting Document
- Appended materials



# Proposed REMS

The REMS includes the necessary elements that support the safe use of the product.

- Goals
- Elements to assure safe use
- Implementation system
- Any materials that are referenced in the REMS
  - Training programs                      -Enrollment forms
  - Patient agreement forms
  - Medication Guide

# REMS Supporting Document

Describes how the program is being implemented

- Whether the element or tools used are compatible with the established distribution, procurement and dispensing systems
- A description of the effectiveness of the proposed program
- Includes metrics that will be used to determine or identify problems with the program and if the goals are being met
- Criteria, methodology or polices that address your management or implementation

# Conclusion

- REMS are a valuable tool for patient safety
- They can employ a variety of tools 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 sponsors (e.g., ANDAs and innovators)

# Information For Industry



Click for:

- [REMS Provision in FD&C Act](#)
- [FDA REMS Website](#)
- [FDA Guidance Documents](#)
- [FDA Webinar: REMS Basics](#)
- [PDF of the slides for today's sessions](#)
- If we did not get to you question, you can always email to us at:



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