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REMS Industry ConsortiumSM

Innovating Patient Safety. Mitigating Risk.

Risk Evaluation and Mitigation Strategies (REMS) 101

REMS 101 – Agenda

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REMS 101 Overview

The Risk Evaluation and Mitigation Strategy (REMS) Industry Consortium (RIC) REMS 101 course was developed by REMS Industry Professionals as a tool to be used by professionals or cross-functional teams to learn about REMS.

What are REMS?



Risk Evaluation and Mitigation Strategies (REMS) are FDA-mandated risk management plans that use **“tools beyond the prescribing information (the package insert) to ensure that the benefits of certain drugs outweigh their risks”***



A REMS may be required by the FDA as part of the approval of a new product, or for an approved product when new safety information arises. New safety information may include:

- Previously unrecognized or unlabeled risk
- New findings concerning a known serious adverse drug reaction (change in frequency, severity, or identification of risk factors)



Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs, and implemented by the product (i.e., no two REMS are exactly alike), although they share a common structure and requirements

What are REMS? (Cont.)

- The Food and Drug Administration Amendments Act (FDAAA) of 2007, signed on September 27, 2007, by President George W. Bush, created section 505-1 of the Food, Drug, and Cosmetic Act (FD&C Act) which authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure the benefits of a drug or biological product outweigh its risks
- Prior to 2007, Risk Management Programs (RMPs) or Risk Minimization Action Plans (RiskMAPs) could be requested by the FDA to mitigate serious risks for a drug product that offered substantial benefits

REMS Overview – Major Policy Milestones

2007

FDAAA Act

A strategy to manage a serious risk known or suspected that may be determined and requested by FDA.

Pre-approval:

- To ensure the benefits of the drug outweigh the risks of the drug, sponsors may be required to submit a REMS

Post-approval:

- New safety information becomes available that requires sponsors to ensure that the benefits continue to outweigh the risks of the drug

2019

CREATES Act

Generic companies can develop a proposed REMS that uses a different, comparable aspect of the ETASU (Parallel-System REMS)

REMS Requirements

- REMS may be required before initial approval of a new drug application or, after the drug has been approved, should FDA become aware of new safety information about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks
- All REMS should include one or more overall goals, and if the REMS has Elements to Assure Safe Use (ETASUs), the REMS must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug and for which the ETASU are required
- REMS generally must include a timetable for submission of assessments of the REMS

REMS Requirements (Cont.)

Failure to comply with the REMS requirements can result in:



Civil penalties



Imprisonment



Misbranding of the drug
(removal from the market)

“A person may not introduce or deliver for introduction into interstate commerce a new drug if...a risk evaluation and mitigation strategy is required...and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements...including requirements regarding assessments of approved strategies”

REMS Requirements (Cont.)

FDA considers the following six factors in making a decision about whether to require a REMS:

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
2. The expected benefit of the drug with respect to the disease or condition;
3. The seriousness of the disease or condition that is to be treated with the drug;
4. Whether the drug is a new molecular entity;
5. The expected or actual duration of treatment with the drug; and
6. The estimated size of the population likely to use the drug

Elements of REMS Programs

REMS programs may have one or more of the following elements:

- **Medication Guide** and/or Patient Package Insert
- **Communication Plan** (direct communication of REMS program with product risk to health care providers)
- **Packaging and Disposal** (mechanism of packaging or disposal to mitigate against a serious risk)
- **Elements to Assure Safe Use (ETASU)**
- **Implementation System** (mechanism of monitoring/evaluating REMS implementation by stakeholders)
- **Assessment** (monitoring and reporting to FDA on the effectiveness of the REMS)



Elements To Assure Safe Use (ETASU)

Section 505-1(f) of the FD&C Act lists certain Elements to Assure Safe Use that may be required if the drug has been shown to be effective, but is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate the specific serious risk(s) listed in the labeling of the product

ETASU may be required for approved products when other elements (e.g., Medication Guide, Communication Plan) are not sufficient to mitigate these risks. The elements to assure safe use must include one or more goals to mitigate a serious risk

Elements To Assure Safe Use (ETASU) Types

ETASU may include one or any combination of the following requirements

Healthcare providers who prescribe the drug have particular training or experience, or are specially certified

Pharmacies, practitioners, or health care settings that dispense the drug are specially certified

Drug be dispensed to patients only in certain healthcare settings, such as hospitals

Drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results

Each patient using the drug be subject to monitoring

Each patient using the drug be enrolled in a registry

REMS Implementation System

Section 505-1(f)(4) of the FD&C Act states that if a REMS includes certain ETASU, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the elements

Examples of Implementation System

- Development of a REMS specific website or call center to facilitate enrollment
- Establishment of electronic database of certified healthcare settings
- Description of how applicable products will be distributed
- Certification of wholesalers and/or distributors who distribute the product to ensure that the product is distributed only to certified or otherwise specified pharmacies, practitioners, or health care settings that dispense the drug, or only to patients who meet the requirements of the REMS

REMS Assessment Report

All REMS are required to submit an Assessment of effectiveness:

- When submitting a supplemental application for a new indication for use
- When required by the REMS (often annually)
- As requested by the FDA, to evaluate whether the approved strategy should be modified to:
 - ensure the benefits of the drug outweigh the risks of the drug; or
 - minimize the burden on the health care delivery system of complying with the strategy

Examples of information that could be provided (actual data depends on Assessment Plan metrics negotiated with the FDA):

- Knowledge, Attitude and Behavior (KAB) survey data that measure prescriber and patient knowledge and understanding of serious risks and safe use conditions
- Summary of adverse events
- Prescriber and Pharmacy compliance
- Usage data
- Number and percentages of patients who were monitored for potential serious adverse events during treatment with the drug

“Each REMS Assessment shall include with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified.”

REMS Industry Participants

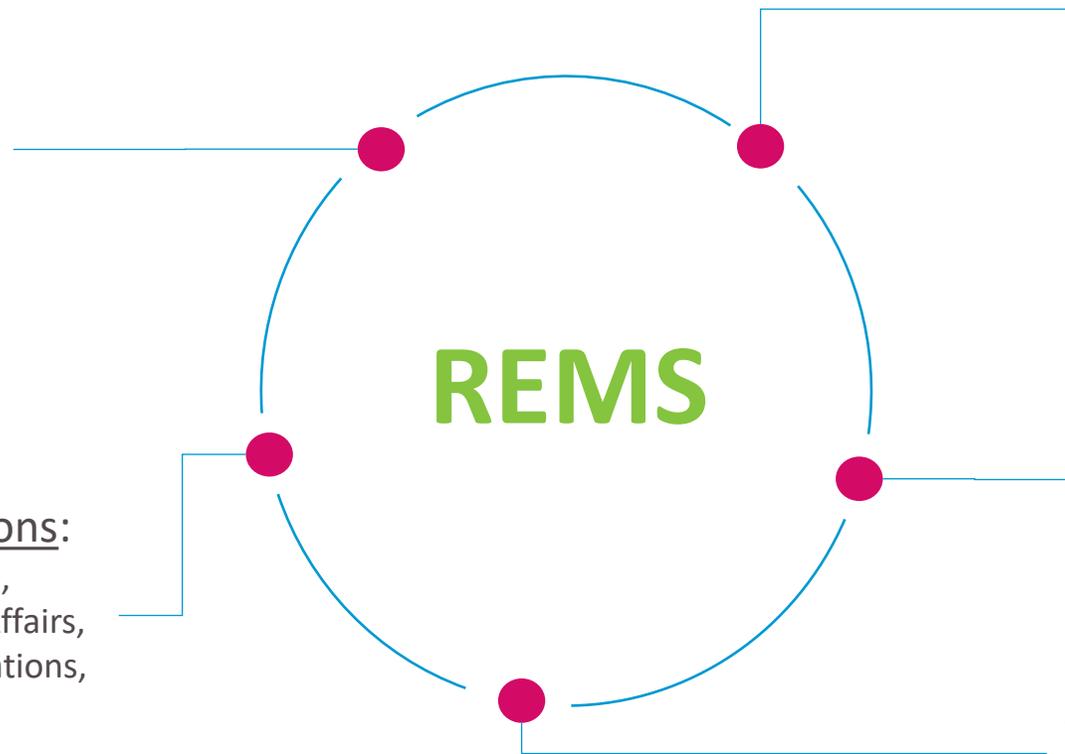
This slide shows some of the many participants from multiple disciplines that are involved in REMS programs.

Vendors / Partners:

Program Management, REMS Administrators, Audits, Surveys, Call Center

Internal REMS Sponsors Functions:

Steering Committee, Pharmacovigilance, Regulatory Affairs, Medical / Scientific Affairs, Quality, Legal Affairs, Commercial Operations, Finance, Information Technology



FDA:

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRM), Office of New Drug (OND) & Office of Generic Drug (OGD)

Stakeholders:

Patients, Prescribers, Retail and Specialty Pharmacies, Hospitals, Wholesalers-Distributions

Advisory Board:

Patient Advocacy, Pharmacy, and Prescribers Associations

REMS Program Models

REMS Program Model	Overview of Model	When FDA Would Require or Recommend
Single REMS	<ul style="list-style-type: none"> A single applicant 	<ul style="list-style-type: none"> FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risk
Bifurcated REMS	<p>A two-part REMS submitted by the Reference Listed Drug (RLD) as a REMS modification:</p> <ul style="list-style-type: none"> Part A: Current REMS applies only to the RLD and would be operational before the first ANDA approval Part B: Shared System REMS that would be operational once the first ANDA is approved 	<ul style="list-style-type: none"> For the FDA to approve the shared system but postpone its operation until approval of the ANDA(s)
Shared System REMS	<ul style="list-style-type: none"> Encompasses multiple prescription drug products and is developed and implemented jointly by two or more applicants Can involve multiple New Drug Applications (NDAs)/Biologics License Applications (BLAs), or Abbreviated New Drug Applications (ANDAs) ANDA applicants may use a “single, shared system” REMS with the RLD or a “different, comparable aspect” of the ETASU (Parallel System [PS] REMS) 	<ul style="list-style-type: none"> An ANDA that references an RLD that has a REMS with ETASU An NDA/BLA that references an NDA/BLA that is subject to REMS with ETASU and has determined that the proposed product also would require the same ETASU Drugs and biologics in a class with similar, serious risks

*References

Topic	Link
Approved Risk Evaluation and Mitigation Strategies (REMS)	https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm
FDA's Role in Managing Medication Risks	FDA's Role in Managing Medication Risks FDA
Guidance Document: Format and Content of a REMS Document	https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm184128.pdf
Guidance Document: FDA's Application of Statutory Factors in Determining When a REMS is Necessary	https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm521504.pdf
Development of a Shared System REMS Guidance for Industry	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-shared-system-rems-guidance-industry
FDA Assessment: Planning and Reporting	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remis-assessment-planning-and-reporting
Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry	Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry FDA