

Risk Evaluation and Mitigation Strategy (REMS): FDA Perspective on What Physicians Need to Know

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The U.S. Food and Drug Administration (FDA) is responsible for the review, approval, and postmarket monitoring of drug products in the United States. All drug product approvals include FDA-approved labeling with information about the indications and usage; dosage and administration; dosage forms and strengths; contraindications, warnings, and precautions; and adverse reactions. FDA labeling also addresses specific populations, clinical pharmacology, findings from clinical studies, and patient counseling.¹

For most drugs, providing health care providers with information about safe and effective use through FDA-approved labeling is sufficient to ensure that the benefits of the drug outweigh the risks. For some drugs, however, additional risk mitigation measures beyond labeling are deemed necessary; these are approved as part of Risk Evaluation and Mitigation Strategy (REMS). These measures can range from communicating risk information to clinicians and patients, to requiring actions that need to be taken prior to prescribing or dispensing the drug.

REMS enables the FDA to approve, and patients to have access to, certain drugs with risks that would otherwise exceed their benefits and may not otherwise be approvable or able to remain on the market.² For example, the FDA has approved several products with REMS programs that clinical trials showed might have serious adverse effects. These adverse events occurred in certain patients around the time of drug administration and could be life-threatening if not recognized and immediately treated. REMS programs were determined to be essential for the safe use of these products and to ensure the benefits outweigh the risks. The REMS programs were designed to ensure

early and direct observation of patients in order to detect these events, and thereby allow clinicians to intervene and prevent poor outcomes. They also provide education about the need to observe patients, the type of monitoring needed, and the treatments to use should an adverse event occur.³⁻⁵ In some cases, REMS also requires certification of prescribers or health care settings (e.g., infusion centers, hospitals, ambulatory care centers) to support these safe use conditions.

As of late 2014, there were approximately 75 REMS programs in place. Of these, 36 (48%) were only informational in nature, composed of letters, websites, and fact sheets describing the specific safety risks identified in the REMS. The remaining 39 REMS programs (52%) also included “elements to assure safe use,” requiring clinicians or health care settings to become certified prior to prescribing and to participate in additional REMS activities, such as training, patient counseling, and monitoring. A listing of approved REMS programs is available on the FDA website at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>.

Physicians play a particularly important role in ensuring that products with serious risks requiring REMS are prescribed and used safely. In addition to understanding the nature of the serious risk, predisposing risk factors, and actions that can be taken to mitigate those risks, the balancing of benefits and risks also needs to be considered for each patient. In this context, appropriate patient selection, patient counseling (e.g., how to use the drug safely, what symptoms should be reported), documentation of safe use conditions (e.g., laboratory monitoring), and adverse event reporting are all important activities. Often, successful management of the serious risks of products with REMS entails additional communication and coordination with other clinicians involved in the treatment of the patient. Details about each REMS program,

including the clinician’s role, can usually be found at a product- or REMS-specific website.

When a REMS program is required, the FDA uses only the elements necessary to ensure the benefits outweigh the risks of the drug. The FDA regularly evaluates the effectiveness and burden of REMS programs, and this information is used to determine if each program is meeting its goals and whether any modifications are warranted. These modifications may include communicating new information to clinicians about the risk, as well as changes in program processes or tools, and other steps being taken to reduce the program burden. Should the FDA determine that, over time, a REMS program is no longer needed, then that program may be eliminated.

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GLOSSARY OF EVIDENCE-BASED MEDICINE AND STATISTICAL TERMS

Term	Abbreviation	Definition
Sensitivity	Sn	Percentage of patients with disease who have a positive test for the disease in question
Specificity	Sp	Percentage of patients without disease who have a negative test for the disease in question
Predictive value (positive and negative)	PV+ PV-	Percentage of patients with a positive or negative test for a disease who do or do not have the disease in question
Pretest probability		Probability of disease before a test is performed
Post-test probability		Probability of disease after a test is performed
Likelihood ratio	LR	LR >1 indicates an increased likelihood of disease, LR <1 indicates a decreased likelihood of disease. The most helpful tests generally have a ratio of less than 0.2 or greater than 5.
Relative risk reduction	RRR	The percentage difference in risk or outcomes between treatment and control groups. Example: if mortality is 30 percent in controls and 20 percent with treatment, RRR is (30 - 20)/30 = 33 percent.
Absolute risk reduction	ARR	The arithmetic difference in risk or outcomes between treatment and control groups. Example: if mortality is 30 percent in controls and 20 percent with treatment, ARR is 30 - 20 = 10 percent.
Number needed to treat	NNT	The number of patients who need to receive an intervention instead of the alternative in order for one additional patient to benefit. The NNT is calculated as: 1/ARR. Example: if the ARR is 4 percent, the NNT = 1/4 percent = 1/0.04 = 25.
Number needed to harm	NNH	The number of patients who need to receive an intervention instead of the alternative in order for one additional patient to experience an adverse event.
95 percent confidence interval	95% CI	An estimate of certainty. It is 95% certain that the true value lies within the given range. A narrow CI is good. A CI that spans 1.0 calls into question the validity of the result.
Systematic review		A type of review article that uses explicit methods to comprehensively analyze and qualitatively synthesize information from multiple studies
Meta-analysis		A type of systematic review that uses rigorous statistical methods to quantitatively synthesize the results of multiple similar studies