

Risk Evaluation and Mitigation Strategies (REMS) Under FDAAA

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1 INTRODUCTION

The highly publicized withdrawal of a number of unsafe drugs from the market over the last several years has led to strong criticism of FDA's ability to protect the public health, resulting in a call for fundamental changes in the United States drug safety system. A report commissioned by FDA in the wake of the Vioxx® withdrawal, and subsequently issued by the Institute of Medicine in 2006, concluded that the science of drug safety needed major improvements. Recommendations included a clarification of FDA's overall authority, an increased attention to safety-related labeling changes, the required registration of clinical trials and results, a restriction of advertising of new drugs, and an increased attention to postmarket monitoring of drugs to minimize patient risk¹⁻³.

On March 25, 2008, new legislation designated as the Food and Drug Administration Amendments Act of 2007 (FDAAA; "the Act") took effect, which directed FDA to develop a systematic, scientifically sound approach to managing the risk-benefit ratio of a drug throughout its lifecycle, with an explicit focus on postapproval safety². The FDAAA is the most comprehensive revision to the Federal Food, Drug, and Cosmetic Act in recent history and creates a significant new vision for drug safety and pharmacovigilance in the United States. The Act grants FDA increased authority to require postmarket epidemiology studies and trials, and to enforce compliance utilizing risk evaluation and mitigation strategies (REMS) as necessary to ensure that the benefits of a drug outweigh its risks to the population.

The purpose of this white paper is to present information characterizing the requirement of the submission of a REMS, one of the key changes related to drug safety as introduced in the FDAAA. The REMS has received perhaps the most attention from the pharmaceutical and biotech industries as it will change several aspects of risk management programs for approved drug products.

2 STATUTORY AUTHORITY FOR REMS UNDER FDAAA

Under Title IX, Subtitle A, Section 901 of the FDAAA, a new statutory framework and authority has been provided for FDA to require a REMS for certain drugs and biologics. The FDAAA permits the Agency to require the applicant of an NDA, Biologics License Application (BLA), Abbreviated New Drug Application (ANDA), and major supplements to submit a proposed REMS as part of the application, prior to approval, if the Agency determines that it is "necessary to ensure that the benefits of the drug outweigh the risks of the drug" (§ 505-1(a)(1)). The Agency may also require REMS after a product's approval if FDA "becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug" (§ 505-1(a)(2)). Furthermore, FDAAA states that drugs and biologics approved prior to the effective date of the Act are "deemed to have in effect an approved risk evaluation and mitigation strategy under Section 505-1 of the Act if there are in effect on the effective date of this Act elements to assure safe use (A) required under [21 CFR 314.520 or 601.42]; or (B) otherwise agreed to by the applicant and [FDA]"

(FDAAA § 909(b)(1)). In short, this new legislation provides FDA with increased authority to require REMS at any point in a drug product's lifecycle based on new safety information.

3 DEFINITION OF REMS PROVISION

A REMS is defined by FDA as a “strategy to manage a known or potential serious risk associated with a drug or biological product.” A REMS will be required of sponsors if FDA determines that a risk minimization intervention is necessary to ensure that the benefits associated with a drug or biological product outweigh its risks. FDA can require a sponsor to submit a REMS when a drug first appears on the market, or postapproval if the Agency becomes aware of new safety information. New safety information may include a previously unrecognized or unlabeled risk, or new findings concerning a known serious adverse drug reaction (e.g., a change in frequency, severity, or identification of risk factors).

According to the statute, FDA's assessment of whether to require a REMS as a condition for approval considers factors such as the size of the population likely to use the drug, the seriousness of the disease or condition that is to be treated by the drug, the expected benefit, the expected or actual duration of treatment with the drug, 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, and whether the drug is a new molecular entity².

A REMS may be conveyed through the use of a number of tools: a Medication Guide, for distribution when the drug is dispensed; a Patient Package Insert, if the insert may help mitigate serious risk of the drug; a communication plan to physicians developed for known or potential serious risks, if FDA determines that the plan may support implementation of an element of the REMS; or “elements to ensure safe use”. These elements may include provisions that healthcare providers who prescribe the drug have particular training, experience, or special certifications; that pharmacies, practitioners, or healthcare settings that dispense the drug be specially certified; that the drug be dispensed only in certain healthcare settings; that the drug be dispensed to patients with evidence of safe-use conditions; that each patient must be subject to monitoring; and/or that patients must be enrolled in a registry (§ 505-1(f)(3) of FDAAA).

Based on the nature and magnitude of safety issues, additional elements of a REMS may include postapproval epidemiological studies to assess signals of serious adverse events or to screen for serious adverse events in expanded populations; postapproval clinical trials to assess signals of serious adverse events; preclearance of, specific disclosures in, and/or restrictions on DTC advertisements; or restrictions on product use or distribution to address a specific expected serious risk (what is currently known).

A drug that has been approved under an ANDA may be subject to fewer REMS components. Generic drugs are only subject to a Medical Guide or Patient Package Insert, and “elements to assure safe use”, if these elements were required for the reference listed drug. For provisions falling under the category of “elements to assure safe use”, FDAAA mandates that generics and innovators must use a single, shared system unless a waiver is obtained from FDA. If there was a communication plan for the reference listed drug, FDA is responsible for implementing the plan when the generic is approved.

If FDA determines that a REMS is required, a timetable for assessing its effectiveness must be submitted. At a minimum, regular assessments of the effectiveness of the REMS are required at

18 months, 3 years, and 7 years after the REMS is approved. Shorter assessment frequencies may also be specified by FDA. However, FDA may stop the assessments after 3 years if the REMS is adequately managing risks. The Act also requires that the REMS be compatible with established systems for dispensing drugs, and that it not be unduly burdensome to patients.

An assessment of and modification to a REMS may be submitted at any time. Assessments are required when submitting an application for a new indication of the drug, when required based on the agreed plan, when requested by FDA based on new information, or within 15 days of notification by FDA that withdrawal of approval may be appropriate under FDA Act Section 505(e).

FDA may also require a REMS for a previously approved covered application if the Agency “becomes aware of new safety information” and makes a determination that a REMS strategy is necessary to “ensure that the benefits of the drug outweigh the risks”. For a postapproval REMS, a sponsor must submit a proposal within 120 days of receiving FDA notification that a REMS is required.

4 REMS EXPERIENCE

Two days following the enactment of the FDAAA on March 25, 2008, FDA published a list of 16 drugs and biologic products that were determined to have “elements to assure safe use” in effect, thus requiring the manufacturers to submit a REMS proposal by September 21, 2008⁴. As of December 2008, FDA has approved 21 additional REMS within eight CDER divisions. On February 6, 2009, FDA notified the sponsors of 24 opioid products with high abuse potential of its intent to develop class-wide REMS for these drugs—the targeted drugs account for more than 20 million prescriptions annually⁵. In addition, as of April 30, 2009, FDA is requiring manufacturers of licensed botulinum toxin products to implement a REMS, as well as strengthen warnings in the product labeling and add a boxed warning regarding the risk of adverse events when the effects of the toxin spread beyond the injection site⁶. The drug products identified by FDA as requiring a REMS are listed in *Table 1*.

Table 1. Drug Products Identified by FDA as Requiring a REMS as of April 30, 2009	
Generic Name	Brand Name
Abarelix	Plenaxis
Alosetron	Lotronex
Ambrisentan	Letairis
Bosentan	Tracleer
Clozapine	Clozaril, Fazacllo ODT
Dofetilide	Tikosyn
Eculizumab	Soliris
Fentanyl PCA	Ionsys
Fentanyl Citrate	Actiq
Isotretinoin	Accutane, Amnesteem, Claravis, Sotret
Lenalidomide	Revlimid

Table 1. Drug Products Identified by FDA as Requiring a REMS as of April 30, 2009	
Generic Name	Brand Name
Mifepristone	Mifeprex
Natalizumab	Tysabri
Small Pox (Vaccinia) Vaccine, Live	ACAM2000
Sodium Oxybate	Xyrem
Thalidomide	Thalomid
Fentanyl	Duragesic Extended Release Transdermal System and generic formulations
Hydromorphone	Palladone Extended Release Capsules
Methadone	Dolophine Tablets and generic formulations
Morphine	Avinza Extended Release Capsules, Kadian Extended Release Capsules, MS Contin Extended Release Tablets, Oramorph Extended Release Tablets, and generic formulations
Oxycodone	OxyContin Extended Release Tablets and generic formulations
Oxymorphone	Opana Extended Release Tablets and generic formulations
Botulinum Toxin Type A	Botox and Botox Cosmetic
Botulinum Toxin Type B	Myobloc
Abobotulinum Toxin A	Dysport

5 RISK MANAGEMENT AND REMS

The concept of using risk management programs or Risk Minimization Action Plans (RiskMAPs) to maximize safety as part of the drug approval process is not new; FDA has been requesting that sponsors submit RiskMAPs for more than 20 years⁷. A RiskMAP is a strategic safety program that is designed to meet specific goals and objectives in minimizing risks through the use of product labeling, education, outreach, and reminder prompting systems. The basic concept of a RiskMAP will not change significantly under the FDAAA; however, the new legislation provides the Agency with statutory authority to require a REMS at any point in a drug's lifecycle based on new safety information. This new data may come from adverse event reports, clinical trials, postapproval studies, reviews of existing data, or the medical literature.

6 IMPLICATIONS OF REMS REQUIREMENT FOR SPONSORS

As considered from a sponsor's perspective, the implementation of the FDAAA and REMS requirement will most likely cause drug lifecycle management to become more costly, complex, and time-consuming. More resources will likely need to be devoted to safety, regulatory, risk management, and epidemiology departments. In addition, new drug approvals will require more time, advertising and labeling may be restricted, and products may require additional postapproval studies or REMS.

The encompassing changes to drug safety as legislated in the FDAAA will also have an impact at FDA because the Agency will be charged with balancing oversight of drug development with the

monitoring of drug safety postapproval. This will also entail the need for increased staffing and planning at the federal level.

7 VIOLATIONS OF REMS PROVISIONS

Under the FDAAA, FDA has been granted enforcement authority for violations of the REMS provisions. The Agency may impose civil monetary penalties, the drug or biological product can be deemed misbranded, and/or FDA may obtain injunctive relief. The FDAAA states that the penalties may not exceed \$250,000 per violation, or \$1,000,000 for all violations adjudicated in a single proceeding. If a violation continues after the sponsor receives written notice, the penalty is \$250,000 for the first 30 day period (or any portion thereof) that the violation continues, not to exceed \$1,000,000 for any 30 day period and not to exceed \$10,000,000 for all violations adjudicated in a single proceeding. In determining the amount of a civil penalty, FDA may take into consideration whether the sponsor or company is making efforts to correct the violation.

8 FDA ASSISTANCE IN REMS PREPARATION

FDA has not yet prepared formal guidance documents to assist sponsors in the preparation of a REMS; however, FDA is presently developing guidances for the industry to clarify the expectations and objectives of a REMS, when FDA would require a REMS, and to specify criteria for utilizing specific REMS tools. Currently, when FDA notifies a sponsor that a REMS is required, a template is appended to the request that details the format for a REMS and the expected elements to be included in the response.

9 REFERENCES

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6. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149574.htm>
7. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. *NEJM*, 1995;333(2):101–106.

To obtain more information, or to arrange for preparation and submission of a REMS, please contact Beckloff Associates at: **913.451.3955**, or send an e-mail to **info@beckloff.com**, or visit our web pages at www.beckloff.com.