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Client Alert

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REMS, Risk, and Reward

REMS, while not to be confused with R.E.M., the Athens, Georgia-based rock and roll band, is becoming almost as ubiquitous and as influential on its respective audience. REMS, or Risk Evaluation and Mitigation Strategy, is a new tool that Congress provided the Food and Drug Administration to ensure the safe use of certain types of prescription drug products. REMS is an extension of Congress and FDA's renewed emphasis on drug safety and proactive risk management. FDA may require a drug manufacturer to include a REMS in its new drug application when the agency concludes this is necessary to ensure that the benefits of the drug outweigh the risks of the drug.

On first review, one might conclude that drugs that require a REMS might present an increased liability risk for drug manufacturers because of safety-related concerns. However, REMS, while potentially negatively affecting product sales, might actually help minimize liability risk, if the company follows the conditions described in the program.

1. Regulatory Overview of REMS

On September 27, 2007, President George Bush signed into law the Food and Drug Administration Amendments Act of 2007 (commonly referred to as "FDAAA"), which amended the Federal Food, Drug, and Cosmetic Act (FDC Act). Newly created section 505-1 of the FDC Act authorizes FDA to require certain types of marketing applications to include a REMS if FDA determines that a REMS is necessary to "assure safe use of the drug, because of its inherent toxicity or potential harmfulness." 21 U.S.C. § 355-1. This provision became effective on March 25, 2008. Due to space limitations, we will highlight certain sections of the law.

According to FDA, a REMS program is:

> a strategy to manage a known or potential serious risk associated with a drug or biological product. A REMS will be required if FDA finds that a REMS is necessary to ensure that the benefits of the drug or biological product outweigh the risks of the product, and FDA notifies the sponsor. A REMS can include a Medication Guide, Patient Package Insert, a communication plan, elements to assure safe use, and an implementation system, and must include a timetable for assessment of the REMS. Some drug and biological products that previously were approved/licensed with risk minimization action plans (RiskMAPs) will now be deemed to have REMS.

FDA, "Questions and Answers on the *Federal Register* Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies" (March 2008).

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Elements to assure safe use may require:

1. healthcare providers who prescribe the drug have particular training or experience, or are specially certified;
2. pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified;
3. the drug is dispensed to patients only in certain healthcare settings, such as hospitals:
4. the drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
5. each patient using the drug is subject to certain monitoring; or
6. each patient using the drug is enrolled in a registry.

21 U.S.C. § 355-1(f)(3).

During the new drug approval process, FDA will determine whether a REMS is required. In evaluating whether to require a REMS, FDA must consider:

1. the estimated size of the population likely to use the drug involved;
2. the seriousness of the disease or condition that is to be treated with the drug;
3. the expected benefit of the drug with respect to such disease or condition;
4. the expected or actual duration of treatment with the drug;
5. 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
6. whether the drug is a new molecular entity.

21 U.S.C. § 355-1(a)(1).

If FDA concludes a REMS is needed and notifies the drug sponsor of this decision, the sponsor of the application must submit a proposed REMS and it will be approved when the drug is approved. If a product is already approved and FDA becomes aware of new safety information that suggests a REMS is necessary for that drug, it will require a REMS. 21 U.S.C. § 355-1(a)(2). FDAAA defines "new safety information" as:

> information derived from a clinical trial, an adverse event report, a post-approval study…, or peer-reviewed biomedical literature; data derived from the post market risk identification and analysis system…; or other scientific data deemed appropriate by the Secretary about
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> (A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or
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> (B) the effectiveness of the approved risk evaluation and mitigation strategy obtained since the last assessment of the strategy.

21 U.S.C. § 355-1(b)(3). FDA will not approve a marketing application without a REMS, if required; the agency has issued Complete Response Letters in which sponsors were requested to submit a REMS proposal as a condition for approval.

All REMS must include a timetable for assessing their effectiveness. For a post-approval REMS, sponsors must submit a proposal within 120 days of receiving FDA notification that a REMS is required, and provide status reports at 18 months, three years and seven years after the REMS is approved. FDA plans to issue developing REMS guidance for industry in the future.

On March 27, 2008, FDA identified a number of drugs and biological products that were approved or licensed with such safe use elements (e.g., required by regulation or otherwise agreed to by the sponsor) and considered to have a REMS. 73 Fed. Reg. 16313. To minimize risks, some products, for example, include a Medication Guide, a communication or educational plan for healthcare providers or patients.[1] Since the enactment of FDAAA, FDA has approved additional REMS programs, covering a wide variety of therapeutic areas. The specific restrictions vary among products. FDA has also notified manufacturers of certain marketed products that a REMS is required based upon new safety information. For example, on February 6, 2009, FDA notified sponsors of certain opioid drug products that they will be required to develop a REMS strategy.[2]

In addition, FDAAA requires that FDA conduct regular, bi-weekly screening of its Adverse Event Reporting System database and post a quarterly report of any new safety information or potential signal of a serious risk.[3] Therefore, one can expect more REMS requests as FDA analyzes the safety data relating to drugs on the market.

2. Discussion

A drug company, understandably, would prefer that FDA not mandate a REMS for its product. The costs to implement such a system will result in increased costs for product distribution and marketing, whether to prepare specific communications tools, establish training systems for doctors, create monitoring or registry programs, or design limited dispensing procedures. In addition, mechanisms required to ensure the safe use of the product can negatively affect product sales, whether, for example, due to restrictions on product availability, or a physician's reluctance to prescribe with restrictions or additional responsibilities. REMS is not ideal from a marketing perspective, although it might be necessary to obtain FDA approval of the drug product.

In addition to potential negative distribution and marketing consequences, a REMS program might create an impression on the doctor, pharmacist, and patient that the specific drug product presents a higher safety risk than other products on the market that treat the same disease. And, if an injury or adverse event arises, the product's need for a REMS might heighten its liability exposure and the risk of a lawsuit. That is, there is increased scrutiny because of the drug's risk profile.

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[1] However, FDAAA notes that a drug will not be considered to have a REMS if it has only a Medication Guide, patient package insert, and/or communication plan. 21 U.S.C. § 355-1(e)(2) and (e)(3).

[2] See, e.g., "A Guide to Safe Use of Pain Medicine," FDA Consumer Health Information, Feb. 23, 2009.

[3] 21 U.S.C. § 355(k)(5).

The aforementioned concerns cannot be discounted and are real. Products with REMS present a different level of safety risk; otherwise, FDA would not have required a particular REMS. However, it is important to recognize that, even if FDA imposes such a program for a drug, it nevertheless has concluded that the product remains safe and effective and can be prescribed, albeit with some limitations. FDA has the authority not to approve a product or, if the drug is already on the market, to recommend corrective action or even withdraw approval of the drug. The imposition of a REMS is a delicate balance, which allows a product to be sold because its benefits outweigh the risks, while establishing a system to minimize these risks.

It is also important to recognize that all drugs have inherent safety issues, which require warnings, contraindications, and precautions. REMS actually focuses on the evaluation of a product's risk profile early and often by communicating effectively these risks with healthcare professionals and patients. A REMS might actually help a drug company minimize, even if not completely eliminate, potential liability risks.[4] Recent case law, which has been discussed in other editions of this newsletter, makes clear that preemption and an FDA approval might not immunize a company from liability exposure due to alleged injuries sustained by use of a particular drug, but a REMS program, if followed by the sponsor company, essentially becomes an additional safeguard and protective fence to maximize the product's safe use which, conversely, should help minimize risk.

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[4] In response to an FDA enforcement letter relating to unlawful promotion, Biogen Idec responded that its REMS ensures that patients receive the risk information. The company noted:

> Unlike the other products flagged, Tysabri has a disciplined risk management program in place and no patient in the U.S. can gain access to the drug without formal enrollment in the REMS TOUCH program, so the risks are all clearly explained by the physician before prescribing.