



Drug Policy 101: FDA Risk Evaluation and Mitigation Strategy (REMS)

Over the past couple of decades, pharmaceutical innovation has provided many new treatments for diseases that previously had limited therapeutic options. However, some of these specialty treatments have well-documented side effects (known as adverse events) that must be carefully managed to prevent potentially life-threatening complications. Examples include treatments for catastrophic epilepsy, breakthrough pain medications for cancer patients, and several anti-cancer drugs.

To help minimize the risk of potentially dangerous side effects, Congress authorized the U.S. Food and Drug Administration (FDA) to develop the Risk Evaluation and Mitigation Strategies (REMS) program, which requires pharmaceutical companies to design steps to help patients, caregivers, providers, and other stakeholders mitigate risks. Pharmaceutical companies often have discretion in designating REMS requirements and may implement REMS at their own initiative. While REMS can be a valuable tool to help enhance patient safety, some manufacturers have exploited the program to keep lower-cost generic versions of their products off the market. They have also used REMS to restrict distribution to certain specialty pharmacies under exclusive contract so that their pricing power is maintained.

Members of Congress have introduced two bills to help address the anticompetitive behavior, both of which would result in significant consumer and government savings.

REMS Overview

In 2007, Congress enacted the *Food and Drug Administration Amendments Act (FDAAA)*, which created the agency's REMS program and gave it new authority to ensure safety for certain drugs with known side effects. The FDA may now impose appropriate REMS

as a condition of approval to market and sell a drug. During the approval process for a new drug application (NDA) for a brand name drug or Abbreviated New Drug Application (ANDA) for a generic drug, the FDA may determine REMS are required to ensure the benefits of a drug outweigh the risks. When making this determination, the FDA considers the following factors:

- The size of the population likely to use the drug;
- The seriousness of the disease or condition treated by the drug;
- The expected benefit of the drug;
- The expected or actual duration of treatment; and
- The seriousness of any known or potential adverse events related to the drug and the incidence of such events in the relevant population.

If the FDA has already approved a drug, but post-approval surveillance yields new safety information or adverse events, the FDA can request REMS. The manufacturer of the drug then has 120 days to complete and submit proposed REMS for FDA review.

Common elements of REMS programs include controls on who can prescribe the drug, medication guides for patients, and safe distribution and handling instructions. REMS thus provides a mechanism for FDA approval of specialty drugs with known side effects, through a strategy to ensure the benefits outweigh the risks.

The REMS development process pathway is described in Figure 1.¹ "Sponsor" refers to the pharmaceutical company.

In the document and design phase, the manufacturer is responsible for drafting the REMS to meet FDA drug safety requirements. FDA then reviews

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**Figure 1:
REMS Development
Process Pathway**



¹ U.S. Food and Drug Administration, Center for Drug Evaluation & Research-hosted webinar titled: Submitting Risk Evaluation and Mitigation Strategies (REMS) in Structured Product Labeling (SPL) Format: What You Need to Know, August 24, 2016.

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the manufacturer's submission. The manufacturer then implements the REMS through packaging and distribution materials. Distributors, dispensers, institutions, prescribers and patients then adopt the manufacturer's REMS. The manufacturer must also assess the effectiveness of the REMS and submit any necessary modifications for review by FDA.

As of September 2016, 74 drugs were subject to REMS; 42 included an additional requirement known as "elements to assure safe usage" (ETASU). These additional ETASU requirements are designed to reduce the risk of a specific serious side effect listed on the drug's label. ETASU requirements can include any of the following:

- Requiring prescribers to have specific training/experience;
- Requiring pharmacies, practitioners or healthcare settings that dispense the drug to be specially certified;
- Providing patient or caretaker consultation for every fill;
- Obtaining and maintaining confirmation and authorization numbers;
- Tracking each dispensing to adhere to quantity restrictions;
- Ensuring appropriate documentation is received;
- Limiting dispensing to certain healthcare settings (i.e., infusion settings, hospitals);
- Ensuring that drug is dispensed only with evidence of safe-use conditions (e.g., laboratory test results);
- Subjecting each patient using the drug to monitoring; or,
- Requiring each patient using the drug to be enrolled in a registry.¹

REMS in Practice & Anticompetitive Behavior

While the intention of the REMS program was to improve patient safety, unforeseen issues created patient access challenges and made it more difficult for lower-cost generic versions of drugs subject to REMS to enter the market. First, the administrative burden REMS place on providers and pharmacists has complicated patient access to many important specialty drugs. For example, biopharmaceutical Celgene's REMS for lenalidomide (Revlimid®) is 100 pages long,² which has delayed patient access due to the additional, complex requirements for prescribers, institutions, distributors and dispensers. Such burdens could potentially

be alleviated by requiring drug manufacturers to involve other stakeholders in the REMS development process.

REMS with ETASU requirements have raised concerns that some restrictions on distribution do not lead to improved patient safety and instead provide an avenue for anticompetitive behavior by drug manufacturers. For example, drug manufacturers sometimes use a REMS to restrict which entities can supply and dispense the drug to third-party specialty pharmacies of their choice, thereby protecting the high prices by exploiting limited access to their products.

Brand-name manufacturers have also used REMS as a reason not to provide samples to generic drug manufacturers. Manufacturers hoping to make a generic version of a drug must submit studies to FDA demonstrating bioequivalence to the branded product. To carry out these tests, generic manufacturers must acquire product samples from the brand manufacturer. In most cases, if brand-name drug manufacturers will not provide samples, generic manufacturers could just purchase the drug themselves from a wholesaler. However, because a drug with REMS with ETASU requires distribution by a specific manufacturer in addition to other limitations, generic manufacturers are limited to receiving samples directly from the brand manufacturer.

In response to this anticompetitive behavior, FDA published sub-regulatory guidance in December 2014 outlining a process for generic manufacturers to request a letter from FDA mandating brand manufacturers to send samples.³ Unfortunately, this has not provided relief for generic manufacturers, as their brand-name counterparts continue to refuse to provide samples based on state products liability legislation and tort law.

Members of Congress have introduced two bills to help address the anticompetitive behavior: the *Fair Access For Safe and Timely (FAST) Generics Act* and the *Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act*. Both bills would require brand manufacturers to provide samples of their products to generic manufacturers for the purpose of conducting bioequivalence studies under the threat of suffering legal penalties, including damages. Both bills would result in significant consumer and government savings by allowing lower-cost generics to enter the market faster. The non-partisan Congressional Budget Office (CBO) estimates that the *FAST Generics Act* would save \$2.35 billion and the *CREATES Act* would save \$3.3 billion for the federal government over a 10-year period.

2 Barlas, S., FDA Intensifies Drive to Reduce REMS Burdens: The Key Objective Is to Ease Workflow Obstacles for Pharmacists, P&T, Vol. 41, No. 2, February 2016.

3 How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD, Available www.fda.gov.

4 Policy Proposal: Improving Generic and Biosimilar Developer Access to Brand Pharmaceutical Samples. The PEW Charitable Trusts, May 30, 2017.