

Using a Drug-Safety Tool to Prevent Competition

Ameet Sarpatwari, J.D., Ph.D., Jerry Avorn, M.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

In 2007, the Food and Drug Administration Amendments Act (FDAAA) created an important new tool for dealing with drugs that have potential safety problems: the Risk Evaluation and Mitigation Strategy (REMS). The aim was to encourage prescribers and patients to use those drugs in such a way that their benefits would outweigh their risks. Troubling cases have emerged, however, in which this tool has been used to hinder competition from generic drugs — an unintended consequence that suggests that Congress may need to revisit its design.

A REMS is a program organized by the drug's manufacturer to provide safeguards for the use of certain high-risk medications. It can vary in complexity from the issuing of medication guides or other means of educating prescribers, patients, or both about

18 months, 3 years, and 7 years after REMS approval; if the FDA determines that the safety problem has been properly managed or is not causing substantial patient harm, it can remove the REMS requirement.

Though sometimes criticized for being onerous and costly to manufacturers, REMS requirements have also been hailed as a means for the FDA to approve important new drugs that might otherwise have been rejected because of a worrisome safety issue identified in preapproval testing. Indeed, in the past 6 years REMS programs have become common, and approximately half of existing REMS programs (39 of 73) include the more complicated elements described above.

As REMS programs have proliferated, controversy has arisen over their effects on the ability of generic drug manufacturers

manufacturers “use a single, shared system” for risk mitigation unless the brand-name company's system is too burdensome or is protected by a patent.¹ Shared REMS programs for potentially dangerous drugs made by multiple manufacturers could produce uniform and predictable oversight systems and better prevent adverse patient outcomes. Some manufacturers, however, have called on the FDA to provide more guidance regarding the development of shared REMS programs, resulting adverse-event reporting, and cost-sharing responsibilities.²

Despite their congressional mandate, REMS systems have been invoked to forestall the market entry of generic drugs in a few prominent cases. One strategy used by brand-name drug manufacturers was to invoke the existence of a REMS system as a rationale for refusing to supply their products to generic drug companies for the basic studies necessary for demonstrating bioequivalence.³ Actelion, for example, recently sued two generic drug companies so that it would not have to provide samples of bosentan (Tracleer), an endothelin-receptor antagonist used to treat pulmonary hypertension. The company contended that its distribution of bosentan is restricted to pharmacies certified under the Tracleer Access Program, which requires education, counseling, and monthly follow-up of enrolled patients for liver function and pregnancy tests, and that it therefore could not provide potential competitors

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the drug to more complicated “elements to assure safe use.” Such elements may include mandatory training or certification for prescribers and pharmacies; person, place, and time restrictions on dispensing; and targeted patient follow-up and testing relying on the establishment of registries. Formal evaluations are required at

to prepare their abbreviated new drug applications and on the availability of generic drugs after a brand-name drug loses its market exclusivity. In the FDAAA, Congress specified that REMS requirements should not be used to “block or delay approval” of generic drugs and mandated that brand-name and generic drug

Examples of Patented REMS Programs and Their Characteristics.						
Drug	Manufacturer	Indication	Selected Safety Concerns	REMS Program	REMS Highlights	REMS Patent Expiration Dates*
Alvimopan (Entereg)	Cubist	Bowel-resection surgery with primary anastomosis	Myocardial infarction	Entereg Access Support and Education	Hospital enrollment and protocol implementation to ensure that no patient receives >15 doses and the hospital will not dispense the drug for outpatient use	2030
Sodium oxybate (Xyrem)	Jazz	Narcolepsy	Respiratory and central nervous system depression, diversion	Xyrem Success Program	Physician and patient enrollment, dispensing through a central pharmacy using a centralized database	2022–2024
Thalidomide (Thalomid)	Celgene	Multiple myeloma, leprosy	Birth defects, venous thromboembolism	Thalomid REMS	Physician and pharmacy certification; patient counseling, surveys, and pregnancy testing; and 4-wk limited supply with no automatic refills	2018–2020
Pomalidomide (Pomalyst)	Celgene	Multiple myeloma	Birth defects, venous thromboembolism	Pomalyst REMS		
Lenalidomide (Revlimid)	Celgene	Multiple myeloma, transfusion-dependent anemia, mantle-cell lymphoma	Birth defects, venous thromboembolism	Revlimid REMS		

* Expiration dates were obtained from the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") re-source.

with samples of the drug. The case was settled in February with an undisclosed agreement.

A second REMS-based anti-generic strategy takes advantage of the fact that the FDAAA implicitly authorizes companies to patent their REMS programs. Manufacturers have done so by describing these programs as innovative methods of safely distributing dangerous drugs that are "new and useful methods of conducting business" (see table). Celgene, for example, manufactures thalidomide (Thalomid), which had been approved in 1998 as a treatment for leprosy and in 2006 for multiple myeloma. Because thalidomide is a well-known teratogen, Celgene developed a System for Thalidomide Education and Prescribing Safety and obtained numerous patents related

to that system, including one claiming exclusivity for a method of "delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated."²⁴ The REMS requires prescriber and pharmacy certification, patient registration, and limitations on drug dispensing. It places patients into one of six risk groups, each of which has its own counseling and testing standards. Before a prescription may be issued, patients and prescribers must each complete a phone survey designed to identify risk-increasing behavior.

Because thalidomide was developed in the 1950s, no current patents protect its underlying active ingredient. However, when generic manufacturer Barr Laboratories sought to market a generic version in late 2007, Celgene sued,

alleging that approving Barr's application would infringe Celgene's REMS patents. One potential option would be for Barr to create its own REMS, but Celgene also filed a citizen's petition demanding that the FDA refuse to approve any generic thalidomide, because any non-patent-infringing REMS would pose "unacceptable risks" by "compound[ing] the confusion and burdens associated with thalidomide risk management and mak[ing] it more likely that the system would be compromised."²⁵ In May 2010, Barr withdrew its application to market its generic version of thalidomide, and Celgene dropped its suit, preventing a judicial decision on the merits of its claim.

Since generic drug competition usually leads to sharp decreases in drug costs and the use of lower-

cost generic drugs is associated with greater patient adherence, the use of REMS requirements to block the market entry of generic drugs could well lead to higher health care costs and adverse patient outcomes. This strategy for extending brand-name exclusivity also appears to violate congressional intent in the FDAAA, in which REMS requirements were presented as a means of preventing adverse effects, not preventing competition. Before the Actelion case was settled, the Federal Trade Commission filed an amicus brief arguing that the refusal of a pharmaceutical company to provide samples to its potential competitors may violate federal antitrust law. The FDA has promised to issue guidelines for generic drug companies seeking to obtain a ruling on the safety of their bioequivalency testing protocols, which would authorize brand-name drug manufacturers to supply drug samples without violating their REMS.

The issue of REMS patents is more complicated. The FDAAA's explicit language anticipating the existence of such patents stands in tension with the emphasis on

shared REMS programs. Even if the FDA were to fulfill its promise to promulgate clearer guidelines for the development and implementation of shared REMS programs, the agency would still be powerless to prevent brand-name drug manufacturers from seeking to patent their REMS. Thus, it might be necessary for Congress to revisit the legislation and prohibit REMS patents, or at least restrict brand-name drug manufacturers from invoking REMS patents against potential generic competitors. Although it is understandable that drug companies would seek to protect their intellectual property and creativity in developing a REMS, permitting programs of education, monitoring, and controlled dispensing to be patented by a single company can undermine patient safety once a generic version of the drug is available.

We think that a single, shared REMS system for a given drug would be the best way of seamlessly and consistently providing guidance to prescribers, pharmacists, and patients; preventing adverse events; eliminating unnecessary confusion; and reducing

administrative burdens on all participants. Manufacturers already receive substantial benefits from the REMS system because it facilitates FDA approval of drugs whose widespread availability might otherwise have been delayed pending further testing. The importance of protecting patients' health demands that an efficient and effective risk-management approach be available to both brand-name and generic drug companies.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.

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Comparative Effectiveness Questions in Oncology

Sham Mailankody, M.B., B.S., and Vinay Prasad, M.D.

The high cost of cancer drugs has been criticized by leading academics¹ and lamented in the popular press.² The average price of 1 year of treatment with a new cancer drug now exceeds \$100,000,¹ and the benefits of many of these therapies — often improvement in median survival

on the order of weeks to months — do not appear commensurate with their prices.² Expensive cancer drugs cost society in two ways. First, high prices are borne by payers each time these drugs are prescribed. And second, high prices preclude independent comparative effectiveness

trials that would seek to establish equally effective but cheaper alternatives — thereby protecting the market share of expensive drugs.

Consider abiraterone acetate, an inhibitor of the cytochrome P450 c17 (CYP17) class of enzymes, which are responsible for