



# REMS and Brand-Generic Negotiations

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## Introduction

Balancing the need to incentivize continued investment in innovative new therapies, ensuring that those drugs are safe, and making them as affordable for patients as possible is an imprecise and unquestionably difficult undertaking. It is the type of work that is almost always best left to market forces, but because some drugs are unusually dangerous and can have serious and long-lasting effects, the Food and Drug Administration (FDA) requires companies applying for FDA approval of new, yet potentially dangerous drugs<sup>1</sup> to impose safety protocols, known as Risk Evaluation and Mitigation Strategies (REMS), on their use. These safety measures may be used as a means of keeping competitors out of the market, causing controversy within the pharmaceutical industry. Various proposals to address this controversy, detailed below, have been proposed, but a resolution that balances the interests of all parties has been elusive.

## Background

Before the Food and Drug Administration Amendments Act of 2007, manufacturers of unusually dangerous drugs (typically drugs where there is a known or potential serious health risk associated with exposure to the pharmaceutical) were permitted to voluntarily use Risk Minimization Action Plans (RiskMAPs) to limit the physical and financial risks associated with marketing the drug. RiskMAPs may include tools such as special provider training and certification programs, informed consent requirements, and enhanced pharmacovigilance programs to reduce the risks of the drug.

In 2007, Congress passed several amendments impacting the FDA, one of which provided authority to require REMS from drug manufacturers if the agency finds these requirements necessary to ensure that the benefits of the drug or biologic outweigh the risks of the product, provided it does not delay competition.<sup>2</sup>

REMS may be initially required by the FDA as part of the [new drug approval process](#), or a REMS may be required later on if any new safety



information arises post-approval. The drug manufacturer has the responsibility of designing the REMS, but the FDA must review and approve all proposals. Brand manufacturers are also required to negotiate a means of sharing their REMS system with generic manufacturers.

REMS can impose safety protocols on more areas of drug production and sale than RiskMAPs, and may include components such as: a Medication Guide; a prescription package insert for patients that includes safety information about the drug; a communication plan; drug-specific safety measures, known as Elements to Assure Safe Use (ETASU), such as requiring physicians to continuously monitor and report on patients' health after receiving the drug; and an implementation system. All REMS must include a timetable to assess whether the system does, in fact, mitigate risks.

In the first implementation year, the use of REMS was relatively uncommon, but by 2014, 40 percent of new FDA approved drugs had REMS requirements (though REMS still apply to only about 6 percent of all FDA approved brand name drugs, as REMs may be removed if they become unnecessary).<sup>3</sup> Among them, ETASU requirements have become increasingly common at around 3 percent of approved drugs: 42 of 74 approved REMS included ETASU.<sup>4</sup> Unlike the other REMS components which are relatively straightforward and are typically shared with patients and providers, ETASU may include patient- and provider-specific information collected by the manufacturer. ETASU may involve enrolling patients in a registry, organizing continuous patient monitoring; documenting continued safe use of the drug; providing prescribing providers with special education, training, or certification; certifying or limiting the providers or facilities that dispense the drug; or ensuring the drug is dispensed only in clinical settings. These systems, which may contain product-specific data and therefore aspects of innovators' intellectual property, have become points of contention when generics begin negotiating access to them.

## **Controversy**

The ability to increase drug safety by limiting who may prescribe or purchase dangerous drugs with REMS has had the effect of erecting a barrier for generic drug manufacturers. Generic manufacturers applying



for an abbreviated new [drug application](#) bypass time-consuming testing to establish safety and effectiveness by demonstrating that their drug is bioequivalent to, or has the same effect on a body as, an FDA-approved drug and therefore has the same level of safety as that FDA-approved drug. This expedited process was designed by a law known as Hatch-Waxman to help make less-expensive generic drugs available to consumers as quickly as possible. In order to prove bioequivalence, the generic manufacturer must first purchase samples of the brand drug on which to run tests for the comparison. However, complying with ETASU designed by the brand before a transfer of the hazardous materials may delay or entirely obstruct generics' ability to establish bioequivalence.

The requirement that brands share their REMS with generic manufacturers has also created an opportunity for brand manufacturers to delay their competition's entrance into the market by drawing out negotiations over the exchange of intellectual property. In some cases, a compromise position, for example, to allow for the transfer of the brand drug to the generic company under certain conditions, is not easily reached and the generic manufacturer may apply to the FDA for a waiver from the shared system requirement. In fact, this breakdown in negotiations occurs so frequently only about 8 percent of FDA-approved REMS have the intended shared system. Furthermore, the legal precedent determining what circumstances entitle a generic to a waiver is frustratingly unclear and requires legislative clarification.<sup>5</sup>

Generic manufacturers object to the use of the safety regulations by brand manufacturers to effectively delay market competition, and even the Federal Trade Commission (FTC) has conceded that the REMS requirements have created a "unique regulatory framework [...that] may be exploited to thwart generic competition."

One study estimated that up to \$5.4 billion in drug savings is lost annually because of delayed market availability of generic drugs.<sup>6</sup> With the increasing use of [biologics](#) and biosimilars – which are more difficult to produce than single-molecule drugs – generic producers worry that the cost of delays could grow significantly in future years.

Brand name and biologic manufacturers, on the other hand, argue that the \$5.4 billion in "lost savings" is not lost, but rather the normal cost of



purchased drugs to compensate for the cost of bringing a novel drug to market. The research and development and FDA approval processes can be long and expensive, and a period of market exclusivity is normal and necessary to incentivize continued growth and innovation. Problems arise, however, when that exclusivity is artificially extended so long that it begins to have negative consequences on access.

Brands further emphasize that the REMS system is necessary to protect patient and provider safety- and also to manage the brands' financial liability should someone who subsequently comes in contact with the drugs experience an adverse event. Even before 2007, voluntary safety measures were common when selling or purchasing dangerous pharmaceuticals, and the mandatory REMS requirements for some drugs should not be understood to preclude precautionary measures where REMS are not statutorily required. Until brands' civil liability in negotiated sales to generic manufacturers can be fully understood, as well as any potential anti-trust implications of these deals, brand producers are cautious in their trade deals involving any unusually dangerous pharmaceuticals.

## Proposed Solutions

### *The FAST Generics Act*

Congressional committees of jurisdiction have considered bills that would further amend the Food, Drugs, and Cosmetics Act to limit the extent to which brand innovators could take advantage of REMS and shared systems negotiations to delay market entry of generic competitors. Legislation such as H.R. 2841, introduced in 2015 and known as the FAST Generics Act, has not been considered by the current Congress.<sup>7</sup> However, administrative action in December 2014 addressed some of the generic manufacturers' complaints through FDA guidance.<sup>8</sup> This guidance attempts to assure brand manufacturers that the FDA has a process to review generics' safety protocols and deem them to at least be comparable to REMS. This alternative process has been used at least a dozen times since the guidance was first released.<sup>9</sup>

Despite this action, however, brand manufacturers claim their hesitancy to sell dangerous drugs to some generics manufacturers arises from the fact that FDA guidance is not legislation and does not have the power to



supersede or repeal congressionally enacted legislation or civil liability. It is, according to the brands' argument, unclear what legal liability brands would face if generic competitors encountered adverse events – particularly if the harmful exposure occurred outside a clinical setting. The divergent perspectives and lack of certainty about these liabilities underscore the need for clarifying legislation on this issue.

### *The CREATES Act*

As a result of some brands' continued hesitancy to sell of dangerous drugs, and the failure of past efforts to arrive at a legislative solution that would mitigate brands' liability during these transactions, the Senate Judiciary Committee is considering S. 3056, the Creating and Restoring Equal Access to Equivalent Samples Act (CREATES Act).<sup>10</sup>

The CREATES Act would allow a generic or biosimilar manufacturer to sue for injunctive relief or significant monetary damages if the brand either fails to deliver the requested drug within 31 days of the initial request, or if the brand and generic (or biosimilar) companies are unable to agree on a shared REMS system.

This proposal could provide a way for pharmaceutical companies that are at an impasse during negotiations to resolve their disputes quickly, thereby getting generic drug options to market faster. However, the brands argue it does not adequately address their underlying concern about the conflicting policies regarding brands' responsibilities to provide samples of their products to their competitors versus their responsibility to the public to ensure that no one is exposed to dangerous substances outside of specific, safe settings.

### **Conclusion**

The fact that an increasing number of newly approved drugs are accompanied by REMS requirements should lead Congress to reconsider the impact REMS misuse can have on patients' access to therapies and amend current law accordingly. Any action taken by Congress on this issue should attempt to balance the conflicting objectives of ensuring that more affordable generics enter the market as soon as possible without posing any excessive risks to those who will be taking or otherwise handling those drugs. These important objectives stand starkly at odds with one another,



and as each side attempts to protect those interests, it will be important for Congress to be mindful of whether legislative action is likely to solve these conflicts better than private contracts, or whether continued interference of this sort will ultimately make the innovation and FDA approval processes more difficult and expensive.

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<sup>1</sup> The FDA refers to ‘unusually dangerous drugs’ as those that pose a ‘serious risk’ or results in danger of death, hospitalization, incapacitation, or disruption of the ability to conduct normal life function, congenital anomaly, or birth defect.

<sup>2</sup>[http://www.paragonrx.com/doc/ParagonRx%20White%20Paper\\_REMS%20for%20Generic%20Products\\_16Apr2015.pdf](http://www.paragonrx.com/doc/ParagonRx%20White%20Paper_REMS%20for%20Generic%20Products_16Apr2015.pdf).

<sup>3</sup> <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>.

<sup>4</sup> <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>.

<sup>5</sup> See Prometheus Labs v. Burwell; <http://www.fdalawblog.net/LOTRONEX%20-%20Prometheus%20Voluntary%20Dismissal.pdf>.

<sup>6</sup> [http://www.gphaonline.org/media/cms/REMS\\_Studyfinal\\_July2014.pdf](http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf).

<sup>7</sup> <https://www.congress.gov/bill/114th-congress/house-bill/2841/text>.

<sup>8</sup>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425662.pdf>.

<sup>9</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4721201/>.

<sup>10</sup> <https://www.congress.gov/bill/114th-congress/senate-bill/3056>.