Congressional Research Service
Informing the legislative debate since 1914

IN FOCUS

October 31, 2016

# Risk Evaluation and Mitigation Strategies (REMS) and Generic Drugs

## Background: REMS

The Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA; P.L. 110-85) expanded the risk-management authority of FDA, authorizing the agency to require, under specified conditions, a risk evaluation and mitigation strategy (REMS) for certain drugs. As part of a REMS, a drug manufacturer may be required to provide certain information to patients (e.g., a medication guide) and health care providers, or to impose restriction on a drug's sale and distribution via one or more "Elements to Assure Safe Use" (ETASU). An ETASU is a restriction on distribution or use that is intended to (1) allow access to those who could benefit from a drug while minimizing the risk of adverse events, and (2) block access to those for whom the risks would outweigh the potential benefits. For example, an ETASU could require that pharmacies, practitioners, or health care settings that dispense the drug be specially certified, or that the patient using the drug be subject to monitoring. By requiring a REMS, FDA is able to approve a drug that it otherwise would have to keep off the market due to safety issues. FDA may determine that a REMS is required upon the manufacturer's submission of a new drug application (NDA), after initial approval or licensing, when a manufacturer presents a new indication or other change, or when the agency becomes aware of certain new information.

The law [21 U.S.C.§355-1(i)] requires that a drug that is the subject of an abbreviated NDA (ANDA; i.e., generic drug) and the reference listed drug (RLD; i.e., brand drug) use a single, shared system of ETASU. The Secretary may waive this requirement for the generic drug if (1) the burden of creating a single, shared system outweighs the benefit, or (2) an aspect of the ETASU for the RLD is claimed by an unexpired patent or is a method entitled to protection, and the generic applicant "certifies that it has sought a license for use of an aspect of the [ETASU] for the applicable listed drug and that it was unable to obtain a license."

## Reports of Misuse

A REMS restricted distribution program controls the chain of supply so that the drugs are provided only to patients with prescriptions from authorized physicians or pharmacies under specified conditions. Although the law [21 U.S.C.§355-1(f)(8)] prohibits the holder of an approved new drug or biologics license application (i.e., the brand company, which is the RLD sponsor) from using ETASU "to block or delay approval of an application," FDA, the Federal Trade Commission, generic drug manufacturers, and various physician, pharmacist, hospital and consumer groups have expressed concern that some brand companies are using REMS to prevent or delay generic drugs from entering the market.

To obtain approval of the generic version of a brand-name drug, the product developer must demonstrate to FDA that, among other things, the generic drug is pharmaceutically equivalent (e.g., has the same active ingredient(s), strength, dosage form, and route of administration) and bioequivalent (e.g., absorbed at the same rate and to the same extent) to the brand drug. To conduct the required bioequivalence (BE) testing, the generic drug developer must obtain a sufficient quantity of samples of the brand-name drug. By restricting distribution of the drug product, the license holder can delay or prevent the generic developer from obtaining samples for testing. Some brand companies have implemented restricted distribution programs for drugs not covered by REMS. Such restricted access programs are generally self-imposed rather than FDA-mandated.

Even when a generic product developer has acquired the necessary samples, conducted the required BE testing, and obtained FDA approval, the difficulties of negotiating a single, shared system of ETASU or obtaining entry into a previously approved system of ETASU can also delay the generic drug from entering the market.

### Role of FDA

Generic companies have looked to FDA to intervene when an RLD sponsor has refused to sell a drug to an eligible drug developer for testing purposes, citing the REMS with ETASU as justification. In December 2014, FDA issued draft guidance, *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD*. This guidance outlines the steps that a generic drug developer should take to obtain a letter from FDA to the RLD sponsor, indicating the generic drug applicant's proposed protocol is as safe as the REMS and that it would not be a violation of the REMS to provide the product samples for BE testing. However, some generic manufacturers have reported that these practices are continuing even after FDA has issued such letters.

## Congressional Action

In the 114th Congress, two bills to keep brand companies from using REMS to prevent or delay generic drugs from entering the market have been introduced: the Fair Access for Safe and Timely Generics Act of 2015 (or the FAST Generics Act of 2015 [H.R. 2841]) and the Creating and Restoring Equal Access to Equivalent Samples Act of 2016 (or the CREATES Act of 2016 [S. 3056]). This section provides an overview of the two bills, as well as a comparable bill from the 112th Congress, but not a comprehensive summary.

### H.R. 2841

The House bill seeks to generally limit a "license holder" (defined as the holder of an approved new drug or biologics license application) of a covered product (i.e., a drug, biologic, or combination thereof, as specified) from restricting its availability for testing purposes by an eligible product developer. Among other things, it would allow the developer to seek authorization from the Secretary to obtain a covered product subject to a REMS with ETASU; would specify the procedure for obtaining authorization from the Secretary and access to the product; and would require the license holder to publicly designate at least one wholesaler or specialty distributor to fulfill product requests, with specified disclosure restrictions. It would allow the Secretary to prohibit or limit the transfer of a product if it would present an "imminent hazard" to public health. It would also exempt the license holder from liability for any claim arising out of an eligible product developer's "failure to follow adequate safeguards during development or testing activities."

In addition, the bill would generally prohibit a license holder from taking any steps to impede the development of a single, shared system of ETASU or the entry of a product developer into a previously approved system of ETASU. It would require license holders to negotiate in good faith toward a single, shared system, but would allow the Secretary to waive the requirement for a single, shared system if the product developer is unable to finalize terms with the license holder. Further, the legislation would also allow an eligible product developer that is injured based on certain violations of the legislation to sue the license holder for injunctive relief and damages.

### S. 3056

Like the House bill, the Senate bill would also establish a mechanism for generic drug manufacturers to obtain the covered product for testing. The legislation would allow the generic product developer to bring a civil action against the license holder for failure to provide the product developer sufficient quantities of the drug on "commercially reasonable, market-based terms." If the product developer prevails in the case, the license holder would generally be required to (1) provide to the product developer, without delay, sufficient quantities of the product, as specified, and (2) award to the developer attorney fees and costs related to the lawsuit, as well as a monetary amount, as specified.

The Senate bill would also allow an eligible product developer to bring civil action against the license holder for failing to reach a single, shared system of ETASU, or for refusing to allow the product developer to join into a previously approved system. If the product developer prevails in such a lawsuit, the license holder would be required to (1) with the approval of the Secretary, enter into a single, shared ETASU with the developer or allow the developer to join a previously approved system, or (2) demonstrate that the Secretary has waived the requirement for a single, shared system. It would also require the license holder to award to the developer attorney fees and costs associated with the litigation and a monetary amount, as specified. The Senate bill contains the same limitation of liability provision as the House bill.

### REMS Legislation and Cost-Savings

Although legislation aimed at reforming FDA REMS has been discussed as a means of reducing healthcare spending, CRS is not aware of any cost estimates (from CBO or other entities) that indicate how H.R. 2841 or S. 3056 would function as such. However, while CBO has not scored these two bills (as of the date of this In Focus), the agency has scored a comparable provision from the 112th Congress—Section 1131 "Drug Development and Bioequivalence Testing" of S. 2516, an early iteration of the Food and Drug Administration Safety and Innovation Act (FDASIA; P.L. 112-144). Like H.R. 2841 and S. 3056, Section 1131 would have generally prohibited the use of ETASU to restrict availability of a covered drug for BE testing by an eligible product developer, as specified, and it would have allowed the developer to seek authorization from the Secretary to obtain a covered drug; it would not have addressed the issue of developing a single, shared system of ETASU. Unlike H.R. 2841 and S. 3056, the definition of "covered drug" under Section 1131 is narrower and would have included only a drug or biologic subject to a REMS with ETASU, as compared to H.R. 2841 and S. 3056, which seek to generally limit a license holder from restricting for BE testing both covered products subject to REMS with ETASU and covered products not subject to REMS with ETASU. In May 2012, CBO estimated that the implementation of Section 1131, with other provisions in S. 2516 aimed at reducing barriers to market entry for lower-priced drugs, would have reduced direct spending for mandatory health programs by $753 million over the 2013-2022 period. Section 1131 was ultimately not included in the final version of the bill signed into law as FDASIA.

## Stakeholder Concerns

The generic drug industry has generally supported congressional efforts to prevent the use of restricted distribution programs from delaying generic entry, as have other stakeholders looking to increase competition to reduce drug prices. A 2014 study sponsored by the Generic Pharmaceutical Association (GPhA) estimated that misuse of REMS and other restricted distribution programs costs the United States $5.4 billion annually, with the federal government bearing a third of this burden. While some say that legislation such as S. 3056 is critical to maintaining pharmaceutical competition, other stakeholders, including the brand pharmaceutical lobby, oppose the Senate bill, arguing that REMS are a necessary regulatory tool for protecting patient safety. During the June 2016 Senate Judiciary Subcommittee hearing on S. 3056, one testimony expressed concern that the Senate bill does not establish robust criteria that product developers must satisfy to protect patients and individuals who come into contact with the drug during its distribution. A paper from the *Journal of Pharmaceutical Policy and Practice* (2016) argues against such legislation, and discusses the importance of maintaining REMS to ensure that proper safety measures are preserved. Further, others refute claims that REMS impedes generic competition citing that at least nine drugs with strict ETASU provisions have generic competitors.

**Agata Dabrowska**, Analyst in Health Policy

**IF10494**

## Disclaimer