FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development

(name redacted)
Analyst in Health Policy

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Summary

The Food and Drug Administration (FDA) regulates the safety and effectiveness of drug products sold in the United States. The statutory standard for FDA approval is that a drug is safe and effective for its intended use. FDA's determination that a drug is safe does not signify an absence of risk but rather that the drug's clinical benefits outweigh its known and potential risks.

For most drugs, FDA has generally considered routine risk minimization measures to be sufficient; for example, updated labeling based on new information from postmarket surveillance. In certain cases, however, the agency has recommended or required additional measures to minimize drug risk. Early risk management programs at FDA, voluntarily instituted by manufacturers, included elements such as education for patients and providers, and restrictions on distribution. In 2007, the FDA Amendments Act (FDAAA) expanded the risk management authority of FDA, authorizing the agency to require for certain drugs, under specified conditions, risk evaluation and mitigation strategies (REMS). REMS is a required risk management plan that uses risk mitigation strategies beyond FDA-approved professional labeling. 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 (e.g., a communication plan) or to impose restriction on a drug's sale and distribution via one or more "Elements to Assure Safe Use" (ETASU).

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 prohibits the holder of an approved new drug or biologics license application (i.e., the brand company) from using ETASU "to block or delay approval of an application," FDA, the Federal Trade Commission, generic drug manufacturers, and some Members of Congress have expressed concern that brand companies are using REMS to prevent or delay generic drugs from entering the market. A 2014 study sponsored by the Generic Pharmaceutical Association (GPhA; recently renamed as the Association for Affordable Medicines [AAM]) 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. REMS have come up in the context of user fee reauthorization, with the Director of the Center for Drug Evaluation and Research at FDA testifying that some brand drug manufacturers have used REMS and distribution restrictions to delay or refuse to sell quantities of a brand-name drug to generic product developers, potentially delaying consumer access to less expensive generic drugs. Without the brand-name drug against which to test bioequivalence of the generic product, the generic product developer cannot complete the required application to FDA. Others argue that REMS are rare, and that FDA only requires REMS with restricted distribution for drugs that would otherwise not be allowed on the market due to safety risks.

In the 114th Congress, two bills were introduced to keep brand companies from using REMS to prevent or delay generic drugs from entering the market: 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]). As of the date of this report, neither of these two bills has been reintroduced in the 115th Congress. However, in the 115th Congress, two bills have been introduced that address generic drug development: the Lower Drug Costs through Competition Act (H.R. 749) and the Increasing Competition in Pharmaceuticals Act (S. 297). Both bills contain a provision titled "Study on REMS," which would require GAO to conduct a study on REMS and its implementation; the study would examine, among other things, the "burden associated with REMS," including on generic drug manufacturers."

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Introduction

The Food and Drug Administration (FDA) regulates the safety and effectiveness of drug products sold in the United States. Prior to marketing a drug, a manufacturer must submit to FDA a new drug application (NDA) demonstrating that the drug is safe and effective for its intended use. FDA reviews each NDA with three major concerns: (1) safety and effectiveness in the drug's proposed use; (2) appropriateness of the proposed labeling; and (3) adequacy of manufacturing methods to ensure the drug's identity, strength, quality, and purity.[1] FDA's determination that a drug is safe does not signify an absence of risk but rather that the drug has an appropriate benefit-risk balance for its intended use and population. For most drugs, FDA has generally considered routine risk minimization measures to be sufficient; for example, FDA-approved labeling and postmarket studies. In certain cases, however, FDA has recommended or required additional measures to minimize risk.

This report provides a brief history of FDA drug regulation, describes FDA's early risk management programs, and focuses on the agency's current risk management authorities, specifically risk evaluation and mitigation strategies (REMS). The report also discusses issues that have arisen as a result of REMS, particularly the impact on generic drug competition. It does not discuss antitrust issues raised by restricted distribution systems.

History of FDA Drug Regulation

The regulation of drugs by the federal government began with the Pure Food and Drug Act of 1906, which prohibited the interstate commerce of adulterated and misbranded drugs.[2] The law did not require drug manufacturers to demonstrate safety or effectiveness prior to marketing.

In 1937, a safety incident surrounding the drug Elixir Sulfanilamide generated public support for increased government regulation over drug safety.[3] The following year, the Federal Food, Drug, and Cosmetic Act (FFDCA) was signed into law, requiring a manufacturer to demonstrate, prior to marketing, that a drug was safe.[4] In 1951, the FFDCA was amended to include a prescription-only category of drugs; drugs in this category require health practitioner supervision (due to drug toxicity, potential harmful effects, and/or method of use), compared with over-the-counter drugs, which may be used without a prescriber's authorization, provided that they have an acceptable safety margin, among meeting other conditions.[5] In 1962, the FFDCA was amended again to require a manufacturer to demonstrate that a drug is effective, in addition to safe, for its intended use. This standard became the basis for the current NDA process.[6]

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[1] See CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*.

[2] Federal Food and Drugs Act of 1906 (The "Wiley Act"), P.L. 59-384; 34 STAT. 768 (1906), 21 U.S.C. §1-15 (1934) repealed in 1938 by 21 U.S.C. §329 (a).

[3] In the 1930s, the drug Sulfanilamide, in tablet and powder form, was used to treat streptococcal infections. In 1937, a company in Bristol, Tennessee compounded a liquid form of the drug and sent shipments all over the country. This new formulation called "Elixir Sulfanilamide" had not been tested for toxicity and at the time, the law did not require safety studies for new drugs. More than 100 deaths in 15 states were linked to Elixir Sulfanilamide. See, FDA, "Taste of Raspberries, Taste of Death The 1937 Elixir Sulfanilamide Incident," *FDA Consumer Magazine*, June 1981, https://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/ucm2007257.htm.

[4] FDA, "A History of the FDA and Drug Regulation in the United States," https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandingover-the-countermedicines/ucm093550.pdf.

[5] See CRS In Focus IF10463, *Regulation of Over-the-Counter (OTC) Drugs*.

[6] See CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*.

In 1992, in response to concerns about the timeliness of drug review, FDA and Congress worked together to develop a new revenue source for the agency (user fees) in exchange for performance goals related to drug review times. The resulting legislation, the Prescription Drug User Fee Act (PDUFA, later called PDUFA I), authorized FDA to collect fees from the pharmaceutical industry and use the revenue to support "the process for the review of human drug applications."[7] PDUFA has been reauthorized on four subsequent occasions; with each reauthorization, Congress has expanded the scope of activities covered by user fees.[8] For example, PDUFA III authorized the use of FDA user fees for drug safety and risk management activities; PDUFA IV authorized the agency to require for certain drugs, under specified conditions, a REMS (defined as a required risk management plan that uses risk mitigation strategies beyond FDA-approved professional labeling); and PDUFA V amended the requirements and procedures concerning assessments of approved REMS and their modification. Congressional authorization for PDUFA, as well as the three other FDA medical product user fee programs—medical device, generic drug, and biosimilar—are scheduled to expire at the end of FY2017.[9] Due to the importance of user fees to FDA's budget (43% of FDA's enacted FY2016 total program level), reauthorization of the programs is often considered "must pass" legislation. As Congress generally uses the reauthorization bill to address related FDA regulatory concerns, it will likely serve as an important driver for the ongoing modification of overall agency regulatory policy.

One issue that has been raised in the context of user fee reauthorization is FDA REMS. Specifically, in a March 2017 hearing on generic drug user fee reauthorization, the Director of the Center for Drug Evaluation and Research (CDER) at FDA identified inappropriate use of REMS as one factor that can delay consumer access to less expensive generic drugs.[10] The Director had raised this same issue in a January 2016 hearing on generic drugs.[11] The Federal Trade Commission (FTC), the generic drug industry, and some Members of Congress have expressed similar concerns regarding the misuse of REMS, and in the 114th Congress, two bills addressing the REMS issue were introduced.[12]

Early FDA Risk Management Programs

As aforementioned, prior to marketing a drug in the United States, a manufacturer is required to obtain approval from FDA. The statutory standard for FDA approval is that the drug is safe and effective for its intended use. FDA's determination that a drug is safe does not signify an absence

[7] CRS Report R44750, *FDA Medical Product User Fee Reauthorization: In Brief*.

[8] PDUFA (P.L. 102-571); PDUFA II, Title I of the FDA Modernization Act of 1997 (FDAMA; P.L. 105-115); PDUFA III, Title V of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188); PDUFA IV, Title I of the FDA Amendments Act of 2007 (FDAAA; P.L. 110-85); and PDUFA V, Title I of the FDA Safety and Innovation Act of 2012 (FDASIA, P.L. 112-144). For additional information about each reauthorization, see CRS Report R42366, *Prescription Drug User Fee Act (PDUFA): 2012 Reauthorization as PDUFA V*.

[9] CRS Report R44750, *FDA Medical Product User Fee Reauthorization: In Brief*.

[10] U.S. Congress, House Committee on Energy and Commerce, "Generic Drug User fee Act Reauthorization (GDUFA II) and Biosimilar User Fee Act Reauthorization (BsUFA II), Testimony of Dr. Janet Woodcock, CDER Director, 115th Cong., 1st sess., March 2, 2017, http://docs.house.gov/meetings/IF/IF14/20170302/105631/HHRG-115-IF14-Wstate-WoodcockJ-20170302.pdf.

[11] U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA)*, Testimony of Dr. Janet Woodcock, CDER Director, 114th Cong., 2nd sess., January 28, 2016, see https://www.fda.gov/NewsEvents/Testimony/ucm484304.htm.

[12] 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). These bills are discussed later in the report.

of risk but rather that the product has an appropriate benefit-risk balance for its intended use and population.[13]

Beginning in the 1980s, the first risk management programs for drugs were instituted at FDA. These programs included elements such as education for patients and providers and restrictions on distribution.[14] One example of an early formalized risk management program was the Accutane (isotretinoin) Pregnancy Prevention Program (PPP). In 1982, FDA approved Accutane for the treatment of severe acne. Due to the potential for teratogenicity,[15] warnings against use of the product during pregnancy were included in three sections of the package insert—"warnings," "precautions," and "contraindications—as well as in the patient information brochure.[16] Accutane materials provided to physicians contained warnings about the potential teratogenicity of the drug, and education programs about adverse events related to Accutane. In the summer of 1983, reports emerged of human malformation associated with Accutane exposure. In response to these reports, the Accutane package insert was revised to highlight warnings, and health communication letters (Dear Doctor and Dear Pharmacist letters) were sent to 500,000 prescribers and 60,000 pharmacists to reiterate the information from the "contraindications" section on the package insert.[17]

The Accutane PPP was implemented following a May 1988 Dermatologic Advisory Committee Meeting, and it was the first risk management program introduced by a pharmaceutical company. Elements of the program included a boxed warning; informed consent for female patients; a PPP kit for physicians containing patient information brochures and pregnancy counseling materials for the prescriber; a prescriber tracking survey; and annual and quarterly meetings with FDA.[18] Prior to FDAAA (i.e., 2007), 16 drugs were approved with restrictive risk management programs, including Clozapine (the "No Blood, No Drug" program) and Thalidomide (the "System for Thalidomide Education and Prescribing Safety," program, or S.T.E.P.S.).[19]

In 2002, the Public Health Security and Bioterrorism Preparedness and Response Act (P.L. 107-188) was signed into law. Title V of the law (PDUFA III) reauthorized prescription drug user fees through FY2007, and in exchange for industry user fees, FDA committed to several performance goals, including those related to the agency's risk management activities such as:[20]

- review pre-NDA/BLA meeting packages that include summaries of relevant safety information and industry questions/discussion points regarding proposed risk management plan activities and discuss the need for any post-approval risk management studies;

[13] FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, March 2005, see https://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf.

[14] J Wilkins Parker, FDA Division of Risk Management, Presentation, "Risk Management in the United States," http://www.fda.gov/downloads/drugs/resourcesforyou/healthprofessionals/ucm473163.pdf.

[15] A teratogen is an exposure in pregnancy that can affect fetal development (e.g., cause birth defects).

[16] Roche, Accutane® (isotretinoin) Capsules, "Pregnancy Prevention Program: A Risk Management Program to Reduce Pregnancies during Accutane Treatment", https://www.fda.gov/ohrms/dockets/ac/00/backgrd/3639b1c_06.pdf.

[17] Ibid.

[18] Ibid.

[19] L Choe, Consumer Safety Officer, Division of Drug Information, FDA Office of Communication, Presentation "Risk Evaluation and Mitigation Strategies (REMS)," https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm276838.pdf.

[20] FDA CDER, Manual of Policies and Procedures (MAPP) 6700.1 https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082058.pdf.

- review proposed risk management plan activities included in an NDA/BLA; and
- develop and issue guidance for industry addressing risk assessment, risk management, and pharmacovigilance practices.[21]

Pursuant to the PDUFA III agreement, FDA issued three risk management guidance documents, including a guidance on the development, implementation, and evaluation of risk minimization action plans (RiskMAPs) for prescription drugs products (and biologics).[22] A RiskMAP is defined as a safety program designed to meet specific *goals* (i.e., a desired end result such as a health outcome) and *objectives* (i.e., an intermediate step to achieving goal) in minimizing the known risks of a drug while preserving its benefits (see **Table 1**). A RiskMAP targets one or more safety goals and uses certain tools (e.g., targeted education and outreach) to achieve those goals.[23]

Table 1. Examples of RiskMAP Goals and Objectives

Drug	Goal	Objective
Clozapine	No agranulocytosis	White blood cell monitoring
Thalidomide	No fetal exposure	Pregnancy prevention and monitoring for pregnancy
Lindane	Minimize CNS toxicity and death	No misuse (overdose or extended use)
Dofetilide	Minimize arrhythmia (torsade de pointes)	Dose adjustment in renal impaired, hospitalize patients while initiating therapy

Source: FDA Office of Surveillance and Epidemiology, Presentation, **"**Practical Experience with Risk Management Plans in the US," 2006, see http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm119346.pdf.

While RiskMAPs contained elements similar to REMS (described in the next section), FDA could recommend but not require a sponsor to implement such a safety program.

Risk Evaluation and Mitigation Strategies (REMS)

In 2007, FDAAA expanded the risk management authority of FDA, authorizing the agency to require for certain drugs, under specified conditions, a REMS. Although FDA practice had long included most of the elements that a REMS may contain, FDAAA gave FDA, through the REMS process, the authority for structured follow-through, dispute resolution, and enforcement.[24]

REMS is a required risk management plan that uses risk mitigation strategies beyond FDA-approved professional labeling. FDA may determine that a REMS is required upon the manufacturer's submission of an 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. 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 (e.g., a

[21] In 2005, FDA issued three such guidance documents: *Premarketing Risk Assessment (Premarketing Guidance)*, *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*.

[22] FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, March 2005, see https://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf.

[23] Ibid.

[24] FFDCA §505-1; (21 U.S.C. 355-1). See also CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*.

communication plan) or to impose restriction on a drug's sale and distribution via one or more "Elements to Assure Safe Use" (ETASU). In determining whether a REMS is necessary, the law requires the consideration of the following factors:

- the estimated size of the population likely to use the drug involved,
- the seriousness of the disease or condition that is to be treated with the drug,
- the expected benefit of the drug with respect to such disease or condition,
- the expected or actual duration of treatment with the drug,
- 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
- whether the drug is a new molecular entity.[25]

Elements of REMS

An approved REMS must include a timetable of when the manufacturer will provide reports to FDA to assess the effectiveness of the REMS components; this includes an assessment, at minimum, by 18 months, three years, and in the seventh year after the REMS is approved, or as otherwise specified.[26] The assessment requirement may be removed after three years if FDA determines that the risks of the drug have been adequately identified, assessed, and managed.

In addition to the required timetable of assessments, a REMS may include the following elements:

Patient Information: The REMS may require the manufacturer to develop materials for distribution to each patient when the drug is dispensed. This could be a Medication Guide, as provided for under FDA regulations,[27] or a patient package insert. In 2011 guidance, FDA determined that it was no longer necessary to consider every Medication Guide to be an element of a REMS.[28] The updated FDA policy allowed manufacturers with REMS that included only a Medication Guide and a timetable for assessment (and no ETASU) to request a modification to eliminate the REMS; however, a Medication Guide could still be required under FDA regulations.[29]

Communication Plan: The REMS may require the manufacturer to create a communication plan, which could include sending letters to health care providers; disseminating information to providers about REMS elements to encourage implementation or explaining safety protocols; or disseminating information through professional societies about any serious risks of the drug and any protocol to assure safe use.

[25] FFDCA §505-1(a)(1); [21 U.S.C. 355-1(a)(1)].

[26] FFDCA 505-1(d); [21 U.S.C. 355-1(d)].

[27] 21 CFR part 208.

[28] FDA, *Questions and Answers on Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*, https://www.fda.gov/Drugs/DrugSafety/ucm248459.htm, and FDA Guidance, *Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies*, November 2011, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf.

[29] Ibid.

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 (e.g., regular pregnancy testing for a drug associated with birth defects). By including such restrictions, FDA is able to approve a drug that it otherwise would have to keep off the market due to safety issues.

Implementation System: The REMS may include an implementation system related to ETASU through which the manufacturer may be required to take reasonable steps to monitor and evaluate those in the health care system (e.g., doctors, pharmacists) responsible for implementing the ETASU.[30]

As of March 2, 2017, there were 77 active, approved REMS (see **Table 2** for a breakdown by risk management element).[31] The number of approved REMS has fluctuated over time. A REMS data file available via FDA's website provides information on all of the drugs that have ever been part of a REMS program, including products that are no longer marketed and/or no longer subject to a REMS; the file lists a total of 253 approved REMS, 176 of which were inactive as of March 2, 2017.[32] As aforementioned, in 2011, FDA determined that it was no longer necessary to consider every Medication Guide to be an element of a REMS and subsequently released from REMS drugs that had a Medication Guide as the only risk management element.[33]

Table 2. FDA-Approved REMS

(current as of March 2, 2017)

Medication Guide	Communication Plan	ETASU	Implementation System	Total
37	24	44	37	77

Source: Created by CRS using the FDA approved REMS Database https://www.accessdata.fda.gov/scripts/cder/rems/. These numbers are current as of March 2, 2017.

Note: The columns do not add to a total of 77 because several of the REMS systems include more than one element.

[30] FFDCA §505-1(f)(4); [21 U.S.C. 355-1(f)(4)].

[31] This does not mean there are 77 drugs covered by an approved REMS. FDA can require REMS for an individual drug or for a class of drugs. For example, as explained in the next section, the REMS for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics covers brand-name and generic products formulated with the active ingredients fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Conversely, the REMS for Mifeprex (mifepristone) covers just the one brand drug.

[32] FDA, Approved Risk Evaluation and Mitigation Strategies (REMS), "REMS Data Files and Historic REMS Information," accessed March 2, 2017, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsData.page.

[33] M Cronin, S. Berger, and P. Seligman, "Risk Evaluation and Mitigation Strategies with Elements to Assure Safe Use: Alignment of the Goals with the Tools to Manage Risk," *Therapeutic Innovation & Regulatory Science*, (2014), vol. 48, no. 6, pp. 724-733. S. Worthy, "Don't sell out to safety: a call to preserve evaluation and mitigation strategies to reduce harm to patients and the public in the U.S.," *Journal of Pharmaceutical Policy and Practice*, (2016), vol. 9, no. 2.

Examples of Approved REMS[34]

REMS can be required for an individual drug or a class of drugs. One example of a REMS for an individual drug is the REMS for Mifeprex (mifepristone), used together in a regimen with the drug misoprostol, to terminate a pregnancy through 70 days gestation.[35] The REMS was initially approved in June 2011 and has been updated on subsequent occasions.[36] It includes an ETASU requiring health care providers who prescribe Mifeprex to be specially certified, as specified; an implementation system requiring distributors of Mifeprex to follow specified processes and procedures; and a timetable for submission of assessments.[37] (See **Table A-1** for a list of materials included in the REMS.) The REMS specifies that Mifeprex must be dispensed to patients only in certain health care settings—specifically clinics, medical offices, and hospitals—by or under the supervision of a certified prescriber. Mifeprex may not be distributed to or dispensed through retail pharmacies or other settings not described above.[38]

An example of a REMS that affects an entire class of drugs is the REMS for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics, which covers brand-name and generic products formulated with the active ingredients fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.[39] While opioid drugs are a necessary component of pain management for certain patients and have therapeutic benefits when used properly, they also present serious risks.[40] Past efforts to prevent the misuse, abuse, and overdose of these drugs, such as additional warnings on the label, risk management plans, and inter-agency collaborations, were found to be insufficient. In February 2009, FDA sent letters to manufacturers of ER/LA opioids indicating that a REMS would be required to ensure that the benefits of these drugs continue to outweigh the risks.[41] The REMS for ER/LA opioids was initially approved on July 9, 2012, and has been updated on subsequent occasions. It includes a medication guide, an ETASU providing training to health care providers who prescribe ER/LA opioids, and a timetable for submission of assessments.[42] (See **Table A-2** for a list of materials included in the ER/LA REMS.)

Some drug applications approved prior to the effective date of FDAAA contained ETASUs that were agreed upon by the applicant and FDA; these elements typically appeared in approved RiskMAPs. In March 2008, FDA published in the *Federal Register* a list of products that were deemed to have an approved REMS and directed application holders to submit a proposed REMS

[34] See **Appendix**

[35] FDA, Mifeprex (mifepristone) Information, https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm.

[36] Some drug applications approved before the effective date of the FDAAA REMS provision contained elements to assure safe use and were deemed by FDA to have, in effect, an approved REMS, including Mifeprex, see 73 *Federal Register* 16313, March 27, 2008.

[37] NDA 020687 MIFEPREX (mifepristone) Tablets, 200mg, REMS, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.

[38] Ibid.

[39] FDA, Background on Opioid REMS, https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm187975.htm.

[40] See CRS Report R43559, *Prescription Drug Abuse*.

[41] Ibid.

[42] Extended-Release (ER) and Long-Acting (LA) Opioid Analgesic Risk Evaluation and Mitigation Strategies (REMS), Reference ID: 3992743, https://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_2016-09-30_REMS_Document%20.pdf.

by September 21, 2008.[43] Drugs that had RiskMAPs prior to FDAAA that have transitioned to a REMS include Thalomid (thalidomide), Accutane (isotretinoin), Mifeprex (mifepristone), and Clozaril (clozapine).[44]

Effects of Restricted Distribution Programs on Generic Drug Development

REMS and Generic Drug Development

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act," P.L. 98-417) amended the FFDCA to establish an expedited pathway for generic drugs, allowing a generic drug manufacturer to submit an abbreviated NDA (ANDA) to FDA for premarket review. Rather than replicate and submit data from animal, clinical, and bioavailability studies, the generic sponsor must show that the generic product is pharmaceutically equivalent (e.g., has the same active ingredient(s), strength, dosage form, route of administration) and bioequivalent[45] to the brand-name product, among meeting other requirements (e.g., reviews of chemistry, manufacturing, controls, labeling, and testing).[46]

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 prohibits the holder of an approved NDA or BLA (i.e., the brand company, which is the reference listed drug [RLD] holder)[47] from using ETASU "to block or delay approval of an application,"[48] FDA, the Federal Trade Commission (FTC), generic drug manufacturers, and several physician, pharmacist, hospital and consumer groups have raised concern that some brand companies may be using REMS to delay generic drugs from entering the market by withholding samples needed for bioequivalence testing and by delaying negotiation of a single shared system of ETASU.[49] Brand companies have typically justified their refusal to sell samples by citing safety concerns, particularly that generic firms may not ensure the safe use of these drugs, and that the brand company could be held liable.[50] Some have maintained that negotiations over a single, shared system are complicated and take time.[51]

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[43] 73 *Federal Register* 16313, March 27, 2008. The list included 28 NDAs, ANDAs, and BLAs.

[44] The REMS for Thalidomide was approved in August 2010, Accutane in October 2010, and Clozapine in September 2015; see FDA Presentation, "Risk Management in the United States," http://www.fda.gov/downloads/drugs/resourcesforyou/healthprofessionals/ucm473163.pdf.

[45] Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient/moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See 21 CFR 320.1(e).

[46] See CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

[47] The brand product is called the reference listed drug (RLD) because the generic product ANDA refers to the clinical data in the brand-name drug's NDA.

[48] FFDCA §505-1(f)(8) [21 U.S.C.§355-1(f)(8)]

[49] U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA), Testimony of Dr. Janet Woodcock, CDER Director, 114th Cong., 2nd sess., January 28, 2016, see https://www.fda.gov/NewsEvents/Testimony/ucm484304.htm, and A Brill, "Lost Prescription Drug Savings from use of REMS Programs to Delay Generic Market Entry," July 2014, Matrix Global Advisors, http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf.

[50] D. Tucker, G. Wells, & M Sheer, "REMS: The Next Pharmaceutical Enforcement Priority?" Antitrust, Vol. 28, No. (continued...)

Bioequivalence Testing

To obtain approval of the generic version of a brand-name drug, the generic product developer must demonstrate to FDA that, among other things, the generic drug is pharmaceutically equivalent and bioequivalent 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. Although the generic product developer generally needs samples to conduct BE testing, the law does not require brand manufacturers to provide samples to generic product developers. By restricting distribution of the drug product, the license holder can delay or prevent the generic developer from obtaining samples for testing.

Typically, generic drug companies have obtained necessary samples of brand products from wholesale distributors. However, when a drug is subject to REMS with ETASU and distribution restrictions are in place, the generic product developer is not an authorized entity and, thus, the wholesale distributor of the brand drug would be in violation of the terms of the REMS if they were to sell the samples to an unauthorized party.[52]

Generic companies have looked to FDA to intervene when a brand company 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 brand company, indicating the generic drug applicant's proposed bioequivalence testing protocol is comparably as safe as the applicable REMS ETASU, and that it would not be a violation of the REMS to provide the product samples for BE testing. The FDA letter cannot compel the brand company to sell the samples to the generic product developer, but rather states that the agency finds the safety protections proposed in the bioequivalence protocol to be comparable to the brand company's REMS program.

Per the guidance, when requesting FDA to send such a letter to the RLD holder, the generic drug developer should complete a disclosure authorization form, which authorizes the agency to disclose to the RLD holder the name of the generic drug developer and the active ingredient of the proposed generic drug product, in addition to other potentially confidential commercial or financial information or trade secrets. By signing this letter, the generic drug developer is agreeing to hold FDA harmless for any injury caused by sharing such information with the RLD holder. In electing to involve FDA, the generic product developer authorizes FDA to disclose potentially confidential information to the RLD holder in hopes of acquiring samples for testing, yet the letter from FDA is not legally binding, so the RLD holder may still choose to withhold the samples.[53]

(...continued)

2, Spring 2014. © 2014 by the American Bar Association, https://www.morganlewis.com/news/2014/03/~/media/files/docs/2014/rems-the-next-pharmaceutical-enforcement-priority.ashx.

[51] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Peter Safir, Senior Counsel at Covington & Burlington LLP, 114th Cong., 2nd sess., June 21, 2016 https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Safir%20Testimony.pdf.

[52] Federal Trade Commission, Amicus Brief, Case No. 1:12-cv-05743-NLH-AMD, https://www.ftc.gov/sites/default/files/documents/amicus_briefs/actelion-pharmaceuticals-ltd.et-al.v.apotex-inc./130311actelionamicusbrief.pdf.

[53] FDA, Guidance for Industry, How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD, Draft, December 2014, https://www.fda.gov/downloads/
(continued...)

In a June 2016 testimony before the Senate Judiciary Subcommittee on Antitrust, Competition, Policy, and Consumer Rights, a representative from the generic pharmaceutical manufacturer Amneal testified that in December 2013, the company requested samples of a brand product subject to REMS for purposes of bioequivalence testing. The testimony reports that it took nearly three years to sign a supply agreement, yet four months later, at the time of the hearing, the company had still not received the samples.[54] Brand companies have cited safety and liability concerns as justification for refusing to sell samples. During that same June 2016 hearing, a representative of brand drug companies testified that various safety concerns could arise as a result of certain legislative attempts to make it easier for generic companies to obtain samples (see "The CREATES Act, S. 3056 (114th Congress)").[55] The representative added in his testimony that

> Congress and FDA have long recognized the risks associated with drugs requiring REMS—and particularly the products whose REMS must also include ETASU in order to receive or maintain FDA approval. Examples of such serious safety issues associated with currently approved drugs with ETASU include risks of shortened overall survival, increased risk of tumor progression or recurrence, increased risks of first trimester pregnancy loss and congenital malformations, and central nervous system depression.[56]

Developing a Single, Shared System of ETASU

Current law requires that if a brand drug is subject to REMS, the ANDA (generic drug application) referencing that product is subject to two of the REMS components: (1) the medication guide or package insert and (2) the ETASU, specifically that the ANDA enter into a single, shared system of ETASU with the brand drug.[57] 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 brand drug 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."[58]

As described in an FDA presentation,[59] the process of developing a single, shared system of ETASU begins with the Office of Generic Drugs (OGD), which first notifies the ANDA sponsor of the requirement for a single, shared system via a REMS notification letter. This letter directs

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(...continued)

drugs/guidancecomplianceregulatoryinformation/guidances/ucm425662.pdf.

[54] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Beth Zelnick Kaufman, Assistant General Counsel at Amneal Pharmaceuticals, 114th Cong., 2nd sess., June 21, 2016.

[55] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Peter Safir, Senior Counsel at Covington & Burlington LLP, 114th Cong., 2nd sess., June 21, 2016 https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Safir%20Testimony.pdf.

[56] Ibid.

[57] FFDCA §505-1(i) [21 U.S.C.§355-1(i)]

[58] FFDCA §505-1(i)(1)(B) [21 U.S.C.§355-1(i)(1)(B)]. Drug Manufacturers have been able to patent their REMS programs "by describing these programs as innovative methods of safely distributing dangerous drugs that are 'new and useful methods of conducting business'... 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.'" See A Sarpatwari, J Avorn, & A Kesselheim, "Using a Drug-Safety Tool to Prevent Competition," *NEJM*, vol. 370, no. 16, (April 2014), http://www.nejm.org/doi/pdf/10.1056/NEJMp1400488.

[59] Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Shared System REMS*, http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539368.pdf.

the ANDA sponsor to contact the RLD holder. The ANDA sponsor initiates discussions with the RLD holder regarding the shared system. FDA then hosts a kick-off meeting to convey expectations and facilitate development of the single, shared system. The generic and brand companies may form an industry working group (IWG) to develop a proposal for the single, shared system, providing biweekly updates to the agency. FDA forms a REMS review team comprising members from various offices within CDER; this review team is responsible for tasks such as communicating to the IWG expected timeframes for milestones and for scheduling periodic teleconferences with the IWG. Once the single, shared system proposal is developed, the brand and generic companies submit it to FDA for review. If either the brand or generic company indicates to FDA that the other company in the IWG is not receptive or responsive to developing the single, shared system, the agency may serve as facilitator to aid in reaching a resolution.

The purpose of a single, shared system is to reduce burden for stakeholders by providing a single portal to access REMS materials and other documentation. Doing so would enable prescribers, pharmacies, and health care settings to complete certification and other administrative requirements once rather than separately for the brand and generic drug. However, generic drug companies have reported difficulty in trying to develop a single, shared system with brand companies.[60] Negotiations surrounding shared REMS often include issues such as cost-sharing, confidentiality, product liability concerns, antitrust concerns, and access to a license for elements protected by a patent.[61]

As of March 2, 2017, FDA's database listed 77 approved REMS, 8 of which are shared systems REMS. For example, the Clozapine shared system REMS and the Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS include multiple NDAs and ANDAs.

While the law does provide for a waiver if a single, shared system is not feasible, the agency considers the waiver as an "option of last resort."[62] During the course of negotiations, if FDA or the sponsors believe that a waiver may be necessary, the agency would determine whether the statutory criteria for a waiver have been met; if so, the agency may permit the ANDA sponsor to use a "different, comparable aspect" of the ETASU (e.g., contains the same elements, must achieve the same level of safety).[63]

In a June 2016 testimony before the Senate Judiciary Subcommittee on Antitrust, Competition, Policy, and Consumer Rights, a representative of brand drug companies testified that "negotiations over a single, shared REMS are complicated—in large part because they deal with important safety issues and a complex healthcare system," and that it takes time for parties to reach agreement on "the range of concerns that must be addressed (e.g., REMS design, adverse event reporting protocols, collective standard operating procedures, cost sharing, decision-making

[60] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Beth Zelnick Kaufman, Assistant General Counsel at Amneal Pharmaceuticals, 114th Cong., 2nd sess., June 21, 2016.

[61] Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Shared System REMS*, http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539368.pdf.

[62] Ibid.

[63] Per FFDCA §505-1(i)(1)(B) [21 U.S.C.§355-1(i)(1)(B)], the Secretary may waive the requirement if "the burden of creating a single, shared system outweighs the benefit ... taking into consideration the impact on health care providers, patients, the applicant for the abbreviated new drug application, and the holder of the reference drug product; or an aspect of the elements to assure safe use for the applicable listed drug is claimed by a patent that has not expired or is a method or process that, as a trade secret, is entitled to protection, and the applicant for the abbreviated new drug application certifies that it has sought a license for use of an aspect of the elements to assure safe use for the applicable listed drug and that it was unable to obtain a license."

authority about REMS administration, assessments, and modification, and associated legal issues such as intellectual property and product liability)."[64]

Non-REMS Restricted Distribution Programs

While FDA may require a REMS with ETASU for certain drugs or biologics with known or potential serious safety risks, some brand companies have implemented restricted distribution programs not mandated by FDA. For example, Turing Pharmaceuticals employed a non-REMS restricted distribution system whereby prescriptions could be obtained only from a single source—a specialty pharmacy—and the company could refuse sale to competitors (e.g., generic product developers).[65] Such restricted distribution programs are self-imposed by the company rather than mandated by FDA and have raised antitrust concerns that go beyond the scope of this report.[66]

Issues for Congress

Stakeholders generally agree that ensuring access to safe and effective drugs is important. While REMS has allowed FDA to approve certain drugs that otherwise may have been kept off the market due to safety risks, the implementation of REMS, particularly REMS with restricted distribution, has raised some issues.

The first issue concerns access to samples and whether brand companies are withholding samples for BE testing due to safety reasons or to delay competition. Generic drug companies have reported that brand companies are inappropriately using REMS-restricted distribution systems to prevent product developers from obtaining samples for BE testing and thus delaying market entry of lower cost drugs. In a March 2017 hearing on restricted distribution systems, CDER Director Dr. Janet Woodcock stated that FDA has received about 150 "inquiries" from generic product developers regarding difficulty accessing samples for BE testing.[67] Brand companies have justified their refusal to sell samples by citing safety concerns (e.g., that the generic company may not ensure safe use of the drug), particularly for REMS-restricted distribution drugs that could have serious side effects or are prone to abuse.[68] Brand companies have also expressed concern that they could be held liable for any injuries caused by the generic, which could result in FDA

[64] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Peter Safir, Senior Counsel at Covington & Burlington LLP, 114th Cong., 2nd sess., June 21, 2016 https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Safir%20Testimony.pdf.

[65] A Pollack, "New York Attorney General Examining Whether Turing Restricted Drug Access," October 12, 2015, see http://www.nytimes.com/2015/10/13/business/new-york-attorney-general-examining-if-turing-restricted-drug-access.html?_r=0.

[66] D Lowe, "Martin Shkreli has one idea, and it's a bad one," *Science Translational Medicine,* September 21, 2015, http://blogs.sciencemag.org/pipeline/archives/2015/09/21/martin-shkreli-has-one-idea-and-its-a-bad-one. M Carrier and A Kesselheim, "The Daraprim Price Hike and a Role for Antitrust," *Health Affairs Blog*, October 21, 2015, http://healthaffairs.org/blog/2015/10/21/the-daraprim-price-hike-and-a-role-for-antitrust/.

[67] U.S. Congress, House Committee on Oversight and Government Reform, Subcommittee on Health Care, Benefits and Administrative Rules, *Examining the Impact of Voluntary Restricted Distribution Systems in the Pharmaceutical Supply Chain*, 115th Cong., March 22, 2017.

[68] D. Tucker, G. Wells, & M Sheer, "REMS: The Next Pharmaceutical Enforcement Priority?" Antitrust, Vol. 28, No. 2, Spring 2014. © 2014 by the American Bar Association, https://www.morganlewis.com/news/2014/03/~/media/files/docs/2014/rems-the-next-pharmaceutical-enforcement-priority.ashx.

requiring additional REMS elements or taking further regulatory action against the brand drug.[69] In addition, adverse events associated with the generic could impact the brand company's reputation.[70] As aforementioned, FDA can review the generic product developer's BE protocol and send a letter to the brand company stating that providing samples for BE testing would not be a violation of the REMS; however, FDA does not have the authority to compel the brand company to provide the samples. The FTC has also weighed in on the issue, stating that although the law allows brand-name drug manufacturers to use restricted drug distribution programs in ways that impede generic competition, the Hatch-Waxman Act cannot function as intended if generic drug companies are unable to access samples of brand-name products for the necessary testing.[71]

The second issue concerns entry into a single, shared system of ETASU, and whether delays are a result of complex and time-consuming negotiations or attempts to delay competition. Current law requires that unless waived by the Secretary, the brand and generic products must enter into a single, shared system of ETASU. The purpose of this requirement is to reduce the burden for stakeholders (e.g., health care providers) by providing a single portal to access REMS materials and other documentation. The FDA and generic drug manufacturers have expressed concern that brand companies may be using this requirement to prevent or delay generic drugs from entering the market by impeding development of a single, shared system. In a January 2016 hearing, CDER Director Dr. Janet Woodcock stated that the requirement of a shared REMS system has posed some challenges:

> The statutory requirement that REMS programs that include elements to assure safe use (ETASU) be implemented through a "single shared system" relies on brand and generic companies to agree on such a system before generic drugs may come to market. This is challenging to implement and frequently results in blocking generic competition.[72]

This concern was reiterated at a March 2017 hearing during which Dr. Woodcock identified inappropriate use of REMS as one factor that can delay consumer access to less expensive generic drugs.[73] Brand companies, however, have said that "negotiations over a single, shared REMS are complicated—in large part because they deal with important safety issues and a complex healthcare system" and that it takes time for both parties to reach agreement on issues such as REMS design, adverse event reporting protocols, collective standard operating procedures, cost sharing, decision-making authority about REMS administration, assessments, and modification, and associated legal issues such as intellectual property and product liability.[74] This is consistent with an FDA presentation stating that negotiations surrounding shared REMS

[69] Ibid.

[70] Ibid.

[71] See, for example, Complaint at 4, Mylan Pharm. Inc. v. Celgene Corp., No. 2:14-CV-2094 (D.N.J. April 3, 2014); Complaint for Declaratory Judgment at 7–8, Actelion Pharm. Ltd. v. Apotex Inc., No. 1:12-cv-05743-NLH-AMD (D.N.J. September 14, 2012)

[72] U.S. Congress, Senate Committee on Health, Education, Labor, and Pensions, *Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA)*, Testimony of Dr. Janet Woodcock, CDER Director, 114th Cong., 2nd sess., January 28, 2016, see https://www.fda.gov/NewsEvents/Testimony/ucm484304.htm.

[73] U.S. Congress, House Committee on Energy and Commerce, "Generic Drug User fee Act Reauthorization (GDUFA II) and Biosimilar User Fee Act Reauthorization (BsUFA II)", Testimony of Dr. Janet Woodcock, CDER Director, 115th Cong., 1st sess., March 2, 2017, http://docs.house.gov/meetings/IF/IF14/20170302/105631/HHRG-115-IF14-Wstate-WoodcockJ-20170302.pdf.

[74] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Peter Safir, Senior Counsel at Covington & Burlington LLP, 114th Cong., 2nd sess., June 21, 2016 https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Safir%20Testimony.pdf.

often include issues such as cost-sharing, confidentiality, product liability concerns, antitrust concerns, and access to a license for elements protected by a patent.[75]

Legislative Proposals

Some Members of Congress have expressed concern regarding "tactics that appeared to frustrate the intent of the Hatch-Waxman Act—a law enacted to streamline and expedite the approval process for generic drugs."[76] In the 112th Congress, in response to concerns surrounding misuse of REMS, an early draft of the FDASIA legislation (S. 2516) contained a provision—Section 1131 "Drug Development and Bioequivalence Testing"—that 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. In addition, the provision 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.[77] Section 1131 was ultimately not included in the final version of the bill signed into law as FDASIA. In the 114th Congress, two bills to keep brand companies from using REMS to prevent or delay generic drugs from entering the market were 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). As of the date of this report, neither of these two bills has been reintroduced in the 115th Congress.

However, in the 115th Congress, two bills addressing generic drug development have been introduced—H.R. 749, the Lower Drug Costs through Competition Act, and S. 297, the Increasing Competition in Pharmaceuticals Act. Both bills contain a provision titled "Study on REMS," which would require GAO to conduct a study on REMS and its implementation, examining, among other things, the "burden associated with REMS," including on generic drug manufacturers."

The FAST Generics Act of 2015, H.R. 2841 (114th Congress)

The House bill sought 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[78] (e.g., a generic drug manufacturer). Among other things, the bill would have

[75] Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Shared System REMS*, http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539368.pdf.

[76] U.S. Congress, Senate Committee on the Judiciary, Subcommittee on Antitrust, *"The CREATES Act: Ending Regulatory Abuse, Protecting Consumers, and Ensuring Drug Price Competition,"* Grassley Statement, 114th Cong., 2nd sess., June 21, 2016, see http://www.grassley.senate.gov/news/news-releases/grassley-statement-judiciary-committee-hearing-anti-competitive-tactics.

[77] Although Congress did consider draft language that would have required manufacturers to provide samples to generic product developers, such language was not included in the final bill. The earlier draft of FDASIA stated that "if a drug is a covered drug, no elements to ensure safe use shall prohibit, or be construed or applied to prohibit, supply of such drug to any eligible drug developer for the purpose of developing, or conducting bioequivalence testing necessary to support, an application under [FFDC Act §505(b)(2) or §505(j) or PHS Act §351(k)]." Id.; Food and Drug Administration Safety and Innovation Act, S. 2516, 112th Cong. §1131 (2012).

[78] An *eligible product developer* is defined as a person that seeks to develop a product for approval pursuant to an application approved under FFDCA section 505(b)(2) or 505(j) or for licensing pursuant to an application under section 351(k) of the Public Health Service Act.

- allowed a developer to seek authorization from the Secretary to obtain a covered product subject to a REMS with ETASU;
- specified the procedure for obtaining authorization from the Secretary and access to the product;
- required the license holder to publicly designate at least one wholesaler or specialty distributor to fulfill product requests, with specified disclosure restrictions;
- allowed the Secretary to prohibit or limit the transfer of a product if it would present an "imminent hazard" to public health; and
- exempted 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 have generally prohibited 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. Moreover, the bill would have required license holders to negotiate in good faith toward a single, shared system, but it would have allowed the Secretary to waive the requirement for a single, shared system if the product developer was unable to finalize terms with the license holder. Further, the legislation would have allowed an eligible product developer that was injured based on certain violations of the legislation to have sued the license holder for injunctive relief and damages.

The CREATES Act, S. 3056 (114th Congress)

The Senate bill would have likewise established a mechanism for an eligible product developer to obtain the covered product for testing. The legislation would have allowed the product developer to bring a civil action against the license holder for failure to provide the covered product developer sufficient quantities of the drug on "commercially reasonable, market-based terms." If the product developer prevailed in the case, the license holder would have generally been 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.

In addition, the Senate bill would have allowed 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 prevailed in such a lawsuit, the license holder would have been 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 have also required 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 health care 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 report), the agency has scored the provision from the 112th Congress—Section 1131 "Drug Development and Bioequivalence Testing" of S. 2516—an early

version of the FDASIA legislation (later version S. 3187 passed as 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, compared to H.R. 2841 and S. 3056, which seek to generally limit a license holder from restricting for BE testing (1) covered products subject to REMS with ETASU and (2) 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.[79] Section 1131 was ultimately not included in the final version of the bill signed into law as FDASIA.

Balancing Brand and Generic Pharmaceutical Industry 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; recently renamed as the Association for Affordable Medicines [AAM]) 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.[80] The AAM has expressed support for the CREATES Act, stating it would "provide a clear solution to abusive, anticompetitive business practices that increase costs to the American health care system by impeding patient access to generic medicines."[81] Opponents of changes to the REMS program argue that REMS are rare and that a forced sale provision "would undermine necessary drug safety precautions and create disincentives for the future development and marketing of higher-risk drugs, especially to treat rare disorders, due to liability concerns."[82] At a June 2016 hearing, a witness representing brand companies testified that the CREATES Act would result in safety concerns, and that the bill would not "establish robust criteria that eligible product developers seeking to obtain such a drug must satisfy in order to protect patients and other individuals who come into contact with the drug during its distribution."[83]

[79] Congressional Budget Office (CBO) Cost Estimate, S. 2516 Food and Drug Administration Safety and Innovation Act, May 11, 2012, https://www.cbo.gov/sites/default/files/112th-congress-2011-2012/costestimate/s25160.pdf.

[80] A Brill, "Lost Prescription Drug Savings from use of REMS Programs to Delay Generic Market Entry," July 2014, Matrix Global Advisors, http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf.

[81] GPhA, Letter to Senators Grassley, Leahy, Lee, and Klobuchar, June 14, 2016, http://www.gphaonline.org/media/cms/CREATES_Act_Group_Letter.pdf

[82] S. Worthy, "Don't sell out to safety: a call to preserve evaluation and mitigation strategies to reduce harm to patients and the public in the U.S.," *Journal of Pharmaceutical Policy and Practice,* (2016), vol. 9, no. 2.

[83] U.S. Congress, Senate Committee on the Judiciary, Testimony prepared by Peter Safir, Senior Counsel at Covington & Burlington LLP, 114th Cong., 2nd sess., June 21, 2016 https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Safir%20Testimony.pdf.

Appendix. Examples of Approved-REMS

Table A-1. Mifeprex REMS

Health care providers who prescribe and dispense Mifeprex must:	
To be able to prescribe	• Review the drug's prescribing information. • Complete and submit the Prescriber Agreement Form.
Before dispensing	• Review the Patient Agreement Form with the patient and fully explain the risks of the Mifeprex treatment regimen. • Provide the patient with the Medication Guide. • Complete the Patient Agreement Form with the patient. Provide a completed copy of the form to the patient and retain a completed copy in the patient's record.
Patients who are prescribed Mifeprex must:	
Before receiving	• Review the Patient Agreement Form. • Complete the Patient Agreement Form with the prescriber. • Receive counseling from the prescriber on the risks associated with Mifeprex.
Distributors that distribute Mifeprex must:	
To be able to distribute	• Establish processes and procedures to ensure that the drug is distributed only to clinics, medical offices, and hospitals identified by certified health care providers. • Establish processes and procedures to maintain a distribution system that is secure and confidential. • Establish processes and procedures to maintain a system for proper storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of Mifeprex. • Train all relevant staff involved in distribution of Mifeprex on the REMS Program requirements.
At all times	• Maintain confidential distribution records of all shipments of Mifeprex. • Cooperate with audits carried out by the application holder to ensure that all processes and procedures are in place and are being followed.
Materials	
	• Patient Agreement Form (PDF) • Prescriber Agreement Form (PDF) • REMS document (PDF) • REMS full (PDF)

Source: FDA, Approved Risk Evaluation and Mitigation Strategies (REMS) database, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=35.

Note: The REMS specifies that Mifeprex must be dispensed to patients only in certain health care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Mifeprex may not be distributed to or dispensed through retail pharmacies or other settings not described above.

Table A-2. Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS

Health care providers who prescribe extended-release long-acting opioid analgesic products
• Receive training provided by the accredited CE provider. • Complete the REMS-compliant training, including the knowledge assessment.
Materials
• FDA Blueprint for Prescriber Education with table of product specific drug information • FDA Blueprint for Prescriber Education • Patient Counseling Document (PCD) • Prescriber Letter 1 • Prescriber Letter 2 • Prescriber Letter 3 • Professional Organization/Licensing Board Letter 1 • Professional Organization/Licensing Board Letter 2 • REMS document • REMS full

Source: FDA, Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Shared System REMS, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17.

Author Contact Information

(name redacted)
Analyst in Health Policy
[redacted]@crs.loc.gov , 7-....