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

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Summary

The Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes the Food and Drug Administration (FDA) to regulate 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 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 distribution or use 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 drug application (generally the brand company) from using ETASU to block or delay approval of a generic drug 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. The Director of the Center for Drug Evaluation and Research (CDER) at FDA, for example, has testified that some brand pharmaceutical companies have used REMS and distribution restrictions to impede competition by (1) withholding or refusing to sell samples of the brand drug to the generic company for purposes of bioequivalence testing and (2) prolonging negotiations related to developing a single, shared system of REMS. Effectively, withholding samples prevents the generic company from obtaining data necessary to support an application for approval, while prolonging negotiations of a single, shared system REMS delays approval of the generic application. Others argue that REMS are rare, and that FDA requires REMS with restricted distribution only for drugs that would otherwise not be allowed on the market due to safety risks.

A 2014 study sponsored by the Generic Pharmaceutical Association (GPhA; now called 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.

In the 115th Congress, legislation to keep brand companies from using REMS to prevent or delay generic drugs from entering the market has been introduced: the Fair Access for Safe and Timely Generics Act of 2017 (or the FAST Generics Act of 2017 [H.R. 2051]) and the Creating and Restoring Equal Access to Equivalent Samples Act of 2017 (or the CREATES Act of 2017 [S. 974, H.R. 2212]). Legislation aimed at reforming REMS has been discussed as a means of reducing healthcare spending, although CRS is not aware of any formal cost estimates from the Congressional Budget Office (CBO) or other entities.

Contents

Introduction	1
History of FDA Drug Regulation	1
Early FDA Risk Management Programs	3
Risk Evaluation and Mitigation Strategies (REMS).....	5
Elements of REMS.....	5
Examples of Approved REMS	7
Impact of REMS on Generic Drug Development	8
Bioequivalence Testing	9
Developing a Single, Shared System REMS	10
Non-REMS Restricted Distribution Programs	12
Issues for Congress.....	13
Legislative Proposals	14
The FAST Generics Act of 2017 (H.R. 2051).....	15
The CREATES Act of 2017 (S. 974, H.R. 2212).....	15
REMS Reform and Cost-Savings.....	16
Balancing Brand and Generic Pharmaceutical Industry Concerns	16

Contacts

Author Contact Information	17
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Introduction

The Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes the Food and Drug Administration (FDA) to regulate 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. While this report generally focuses on REMS in the context of generic drug development, the issues discussed are also relevant to biological and biosimilar product development.² This report does not address 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.³ 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.⁴ The following year, the FFDCA was signed into law, requiring a manufacturer to demonstrate, prior to marketing, that a drug was safe.⁵ 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

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

² A biologic is a preparation, such as a drug or a vaccine, that is made from living organisms.

³ 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).

⁴ 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>.

⁵ 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>.

other conditions.⁶ In 1962, the FDCA 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.⁷

The Drug Price Competition and Patent Term Restoration Act of 1984 (“Hatch-Waxman Act,” P.L. 98-417) amended the FDCA to establish an expedited pathway for generic drugs, allowing a generic drug manufacturer to submit an abbreviated new drug application (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 the same as the brand drug (i.e., the reference listed drug [RLD]).⁸ Specifically, the generic product must have the same active ingredient(s), strength, dosage form, and route of administration and must be bioequivalent⁹ to the RLD, along with meeting other requirements (e.g., reviews of chemistry, manufacturing, controls, labeling, and testing).¹⁰

In 2007, the Food and Drug Administration Amendments Act (FDAAA; P.L. 110-85) gave FDA the authority to require for certain drugs, under specified conditions, risk evaluation and mitigation strategies (REMS). REMS is defined as a required risk management plan that uses risk mitigation strategies beyond FDA-approved professional labeling. 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 concerns. One such concern is that certain brand pharmaceutical companies have used REMS to delay competition by refusing generic product developers access to samples needed to conduct the necessary bioequivalence testing to support an ANDA.

In 2012, in response to concerns surrounding misuse of REMS, legislation was introduced that would have generally prohibited the use of REMS to restrict availability of a drug for purposes of bioequivalence testing by a generic product developer; it was not enacted.¹¹ With growing concern over high drug prices, REMS reform came to the forefront again during the 2017 user fee reauthorization, proposed as a way to increase generic product competition and reduce drug prices.¹²

In a March 2017 hearing on generic drug user fees, 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.¹³ The Director had previously raised this same

⁶ See CRS In Focus IF10463, *Regulation of Over-the-Counter (OTC) Drugs*.

⁷ See CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*.

⁸ 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.

⁹ 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 C.F.R. 320.1(e).

¹⁰ See CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

¹¹ An early version of the Food and Drug Administration Safety and Innovation Act (FDASIA; P.L. 112-144), S. 2516, contained a provision—Section 1131 “Drug Development and Bioequivalence Testing”—that would have generally prohibited the use of REMS to restrict availability of a covered drug for bioequivalence testing by an eligible product developer, among other things.

¹² For information about FDA user fees and the 2017 reauthorization, see CRS Report R44750, *FDA Medical Product User Fee Reauthorization: In Brief*, and CRS Report R44961, *FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52)*.

¹³ 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 (continued...) ”

issue in a January 2016 hearing on generic drugs.¹⁴ 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 and 115th Congresses, legislation addressing REMS in the context of generic drug development was introduced.¹⁵ During the House Energy and Commerce full committee markup of H.R. 2430, which was later enacted as the FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52), language targeting misuse of REMS was offered as an amendment to the bill.¹⁶ However, it was withdrawn and ultimately not included in the bill reported out of committee.¹⁷

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 of risk but rather that the product has an appropriate benefit-risk balance for its intended use and population.¹⁸

Beginning in the 1980s, the first risk management programs for drugs were developed at FDA.¹⁹ These programs included elements such as education for patients and providers and restrictions on distribution. 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,²⁰ 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.²¹ 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

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Cong., 1st sess., March 2, 2017, <http://docs.house.gov/meetings/IF/IF14/20170302/105631/HHRG-115-IF14-Wstate-WoodcockJ-20170302.pdf>.

¹⁴ 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>.

¹⁵ 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.

¹⁶ U.S. Congress, House Committee on Energy and Commerce Markup, June 7, 2017, Amendment to H.R. 2430 filed by Rep. Welch (WELCH_01) <http://docs.house.gov/meetings/IF/IF00/20170607/106096/BILLS-115-2430-W000800-Amdt-10.pdf>.

¹⁷ U.S. Congress, House Committee on Energy and Commerce Markup, June 7, 2017, Final Vote Sheet, <http://docs.house.gov/meetings/IF/IF00/20170607/106096/CRPT-115-IF00-Vote002-20170607.pdf>.

¹⁸ FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, March 2005, see <https://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf>.

¹⁹ 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>.

²⁰ A teratogen is an exposure in pregnancy that can affect fetal development (e.g., cause birth defects).

²¹ 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.

prescribers and 60,000 pharmacists to reiterate the information from the “contraindications” section on the package insert.²²

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.²³ 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.).²⁴

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 as²⁵

- review pre-NDA/Biologics License Application (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;
- 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.²⁶

Pursuant to the PDUFA III agreement, FDA issued three risk management guidance documents, including guidance on the development, implementation, and evaluation of risk minimization action plans (RiskMAPs) for prescription drugs products (and biologics).²⁷ 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). A RiskMAP targets one or more safety goals and uses certain tools (e.g., targeted education and outreach) to achieve those goals.²⁸

RiskMAPs contained elements similar to REMS (described in the next section), and while FDA could recommend that a sponsor implement such a safety program, FDAAA gave FDA the explicit authority to require REMS if necessary to ensure the benefits of a drug outweigh the

²² Ibid.

²³ Ibid.

²⁴ L Choe, Consumer Safety Officer, Division of Drug Information, FDA Office of Communication, Presentation “Risk Evaluation and Mitigation Strategies (REMS).”

²⁵ FDA CDER, Manual of Policies and Procedures (MAPP) 6700.1, <https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082058.pdf>.

²⁶ 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)*.

²⁷ FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, March 2005, see <https://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf>.

²⁸ For example, for the drug Thalidomide, the goal was to prevent fetal exposure, and the objective for achieving that goal was through pregnancy prevention and monitoring. For the drug Clozapine, the goal was no agranulocytosis (extremely low white blood cell count), and the objective for achieving that goal was through white blood cell monitoring.

risks.²⁹ Some drug applications approved prior to the effective date of FDAAA contained elements to assure safe use, which typically appeared in approved RiskMAPs. In March 2008, FDA identified and published in the *Federal Register* a list of drug and biological products that were deemed to have an approved REMS and directed application holders to submit a proposed REMS, as specified.³⁰

Risk Evaluation and Mitigation Strategies (REMS)

In 2007, FDAAA expanded the risk management authority of FDA, authorizing the agency to require REMS for certain drugs, under specified conditions. 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.³¹

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 or BLA, as part of the 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 communication plan) or to impose restrictions on distribution or use of the drug via one or more "Elements to Assure Safe Use" (ETASU). In determining whether 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.³²

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.³³ 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.

²⁹ FDA, "FDA's Role in Managing Medication Risks," <https://www.fda.gov/Drugs/DrugSafety/REMS/ucm592672.htm>.

³⁰ 73 *Federal Register* 16313, March 27, 2008. The list included 28 NDAs, ANDAs, and BLAs. Drugs that had RiskMAPs prior to FDAAA that have transitioned to a REMS include Thalomid (thalidomide), Accutane (isotretinoin), Mifeprex (mifepristone), and Clozaril (clozapine).

³¹ FFDCA §505-1 [21 U.S.C. 355-1]. See also CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*.

³² FFDCA §505-1(a)(1) [21 U.S.C. 355-1(a)(1)].

³³ FFDCA 505-1(d) [21 U.S.C. 355-1(d)].

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,³⁴ 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.³⁵ 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.³⁶

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.

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.³⁷

According to FDA’s website, as of January 2018, there are 72 active, approved REMS, of which 45 include ETASU, 10 include only a communication plan, and 17 include only the medication guide.³⁸ The number of REMS has changed over time, and FDA’s website provides information on both the number of active and released REMS (i.e., products whose REMS are no longer in effect).³⁹ As aforementioned, in 2011, FDA determined that it was no longer necessary to consider

³⁴ 21 CFR part 208.

³⁵ 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>.

³⁶ Ibid.

³⁷ FFDCA §505-1(f)(4) [21 U.S.C. 355-1(f)(4)].

³⁸ This does not mean there are 72 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. FDA has announced that immediate-release (IR) opioids would be subject to the same requirements. Conversely, the REMS for Mifeprex (mifepristone) covers just the one brand NDA.

³⁹ FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)*, “REMS Data Files and Historic REMS Information,” accessed January 25, 2018, (continued...)

every Medication Guide to be part of a REMS and subsequently released from REMS, under certain circumstances, drugs that had a only Medication Guide and timetable for submission of assessments.⁴⁰

Examples of Approved REMS

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.⁴¹ The REMS was initially approved in June 2011 and has been updated on subsequent occasions.⁴² 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.⁴³ 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.⁴⁴

An example of REMS that affects an entire class of drugs is the REMS for Opioid Analgesics, which covers brand-name and generic pain-reducing medications that bind to opioid receptors in the body.⁴⁵ 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.⁴⁶ 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. Thus, in February 2009, FDA sent letters to manufacturers of extended-release, long-acting (ER/LA) opioids indicating that REMS would be required to ensure that the benefits of these drugs continue to outweigh the risks.⁴⁷ The REMS for ER/LA opioids was initially approved on July 9, 2012, and has been updated on subsequent occasions. In 2017, for example, FDA announced that immediate-release (IR) opioids would be subject to the same REMS requirements as ER/LA opioids.⁴⁸ The REMS includes a medication guide, an ETASU that requires covered

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<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisData.page>.

⁴⁰ 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.

⁴¹ FDA, Mifeprex (mifepristone) Information, <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm>.

⁴² 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.

⁴³ NDA 020687 MIFEPREX (mifepristone) Tablets, 200mg, REMS, https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf.

⁴⁴ *Ibid.*

⁴⁵ FDA, Risk Evaluation and Mitigation Strategy (REMS) for Opioid Analgesics, <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

⁴⁶ See CRS Report R43559, *Prescription Drug Abuse*.

⁴⁷ *Ibid.*

⁴⁸ FDA, Risk Evaluation and Mitigation Strategy (REMS) for Opioid Analgesics, <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

manufacturers to provide training to health care providers, and a timetable for submission of assessments.⁴⁹

Impact of REMS on Generic Drug Development

The Hatch-Waxman Act created an abbreviated pathway for generic drugs, allowing a generic drug manufacturer to submit to FDA an ANDA, rather than a full NDA, demonstrating that the generic product is the same as the brand drug (i.e., the reference listed drug [RLD]).⁵⁰ To prove sameness, the generic product must have the same active ingredient(s), strength, dosage form, and route of administration as the RLD; be bioequivalent to the RLD; and meet other requirements (e.g., reviews of chemistry, manufacturing, controls, labeling, and testing).⁵¹

Unlike drugs, biologics and biosimilars are generally regulated under the Public Health Service Act (PHSA) and are *licensed* by FDA rather than approved.⁵² A biological product, or biologic, is a preparation, such as a drug or a vaccine, that is made from living organisms. The Hatch-Waxman Act did not provide an expedited mechanism for follow-on biologics, with the exception of follow-on applications submitted for the few so-called “natural source” biologics approved under the FFDCIA (e.g., insulin).⁵³ Because biologics are made from living organisms and feature a more complex structure than chemical drugs, it would be challenging for manufacturers of follow-on products to demonstrate sameness as required under Hatch-Waxman. In 2010, the Biologics Price Competition and Innovation Act (BPCIA) created an abbreviated licensure pathway for biological products that are demonstrated to be “highly similar” (biosimilar) to or “interchangeable” with an FDA-licensed biological product.⁵⁴ A company interested in marketing a biosimilar product in the United States must submit to FDA an application that provides information demonstrating biosimilarity based on data from analytical studies (structural and functional tests), animal studies (toxicity tests), and a clinical study or studies (tests in human patients).⁵⁵ Bioequivalence testing is not required of biosimilar product applicants, but other required testing may necessitate access to samples of the biologic to demonstrate “biosimilarity.” While this report focuses on REMS in the context of generic drug development and approval, stakeholders have raised similar REMS-related concerns for biologics and biosimilars.

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. The law prohibits the holder of an approved application (i.e., the brand company, which is the RLD holder) from using ETASU “to block or delay approval of an application under [FFDCIA] section 505(b)(2) or (j).”⁵⁶ However, FDA, FTC, the Association for

⁴⁹ 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.

⁵⁰ 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.

⁵¹ See CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

⁵² The majority of biologics are regulated under Section 351 of the PHSA [42 U.S.C. §262]

⁵³ For additional information about the regulations of biologics and biosimilars, see CRS Report R44620 *Biologics and Biosimilars: Background and Key Issues*.

⁵⁴ The BPCIA of 2009 was enacted as Title VII of the Patient Protection and Affordable Care Act (ACA, P.L. 111-148).

⁵⁵ PHSA §351(k). See also CRS Report R44620 *Biologics and Biosimilars: Background and Key Issues*.

⁵⁶ FFDCIA §505-1(f)(8) [21 U.S.C. §355-1(f)(8)].

Accessible Medicines (AAM), and others have alleged that some brand companies may be using REMS to delay competition by refusing to sell samples of the brand drug to generic product developers and delaying negotiation of a single, shared system REMS (see the section “Developing a Single, Shared System REMS”).⁵⁷ By withholding samples, the RLD holder is generally able to prevent or delay the generic product developer from conducting the required testing and submitting an application for review; by delaying negotiation of a single shared system REMS, the RLD holder is effectively able to stay FDA approval of the ANDA. Brand companies have typically justified their refusal to sell samples by citing safety concerns, particularly that product developers may not ensure the safe use of these drugs, and that the brand company could be held liable.⁵⁸

Bioequivalence Testing

To obtain approval of the generic version of an RLD, the generic product developer must demonstrate to FDA that, among other things, the generic drug is the same as the RLD. To conduct the required bioequivalence testing, the generic drug developer must obtain a sufficient quantity of samples of the RLD. Although the generic product developer generally needs samples to conduct bioequivalence testing, the law does not require the RLD holder to provide samples to generic product developers.

Typically, generic drug companies have obtained necessary samples from wholesale distribution channels. 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 RLD may be in violation of the terms of the REMS if it were to sell the samples to an unauthorized party.⁵⁹

Generic companies have looked to FDA to intervene when the RLD holder has refused to sell a drug to an eligible product developer for testing purposes, citing the REMS with ETASU as justification. In December 2014, FDA issued draft guidance outlining the steps that an ANDA sponsor should take to obtain a letter from FDA to the RLD holder, indicating the ANDA sponsor’s proposed bioequivalence testing protocol is comparably as safe as the applicable ETASU, and that it would not be a violation of the REMS to provide the product samples for such testing.⁶⁰ The FDA letter cannot compel the RLD holder 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.⁶¹

⁵⁷ 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.

⁵⁸ 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/rem-s-the-next-pharmaceutical-enforcement-priority.ashx>.

⁵⁹ 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.

⁶⁰ 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/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425662.pdf>.

⁶¹ *Ibid.*

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, but the RLD holder may still choose to withhold the samples.⁶² The guidance is specific to ANDA sponsors (i.e., generic drug applicants) and does not address obtaining samples for purposes of biosimilar product testing.

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.⁶³ 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.⁶⁴ 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.⁶⁵

Developing a Single, Shared System REMS

Current law requires that if the RLD is subject to REMS, the generic drug 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 generic and RLD must enter into a single, shared system of ETASU.⁶⁶ The Secretary may waive this requirement for the generic drug if (1) the burden of creating a single, shared system outweighs the benefit, taking into consideration the impact on health care providers, patients, the generic applicant, and the RLD holder, 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.”⁶⁷

⁶² Ibid.

⁶³ 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.

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 Ibid.

⁶⁶ FFDCA §505-1(i) [21 U.S.C. §355-1(i)].

⁶⁷ FFDCA §505-1(i)(1)(B) [21 U.S.C. §355-1(i)(1)(B)]. Drug Manufacturers have been able to patent their REMS (continued...)

As described in FDA presentations, the process of developing a single, shared system REMS begins with the Office of Generic Drugs (OGD), which first notifies the ANDA sponsor of the requirement via a REMS notification letter.⁶⁸ This letter directs the ANDA sponsor to contact the RLD holder. The ANDA sponsor initiates discussions with the RLD holder, and FDA then hosts a kick-off meeting to convey expectations and facilitate development of the single, shared system. The generic developer and RLD holder may form an industry working group (IWG) to develop a proposal for the single, shared system REMS, 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 REMS proposal is developed, the RLD holder and ANDA sponsor 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 a shared REMS, 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, 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,⁶⁹ and generic drug companies have reported difficulty in trying to develop a single, shared system with brand companies.⁷⁰

While the law does provide for a waiver if a single, shared system REMS is not feasible, the agency considers the waiver an “option of last resort.”⁷¹ To date, the agency has issued three such waivers. 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).⁷²

(...continued)

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>.

⁶⁸ Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Single, Shared System REMS*, October 26, 2016, https://www.gphaonline.org/media/wysiwyg/Meetings/Fall_2016/Elaine_Lippmann.pdf, and Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Shared System REMS*, <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539368.pdf>.

⁶⁹ Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Shared System REMS*, <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539368.pdf>.

⁷⁰ 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.

⁷¹ *Ibid.*

⁷² Per FDCA §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 (continued...) ”

In November 2017, as part of FDA’s Drug Competition Action Plan, the agency issued draft guidance to facilitate the submission and review process for shared system REMS.⁷³ The guidance addresses how companies with products in shared system REMS programs can use a single Drug Master File to submit one collective set of files to the agency. According to FDA, the process “eliminates duplicative paperwork for sponsors, and will decrease the volume of forms the FDA’s reviewers must assess.”⁷⁴ CDER plans to publish two guidance documents, *Development of a Shared System REMS* and *Waivers of the Single, Shared System REMS Requirement*, during calendar year 2018.⁷⁵

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 authority about REMS administration, assessments, and modification, and associated legal issues such as intellectual property and product liability).”⁷⁶

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).⁷⁷ 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.⁷⁸

(...continued)

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.”

⁷³ FDA, Draft Guidance, *Use of a Drug Master File for Shared System REMS Submissions*, November 2017, <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm584202.pdf>.

⁷⁴ FDA, Press Announcement, “Statement from FDA Commissioner Scott Gottlieb, M.D. on new steps to improve FDA review of shared Risk Evaluation and Mitigation Strategies to improve generic drug access,” November 8, 2017, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584259.htm>.

⁷⁵ FDA, “Guidance Agenda New & Revised Draft Guidances CDER Plans to Publish During Calendar Year 2018,” January 19, 2018, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417290.pdf>.

⁷⁶ 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>.

⁷⁷ 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.

⁷⁸ 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/>.

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 bioequivalence 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 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 bioequivalence testing.⁷⁹ 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.⁸⁰ Brand companies have also expressed that they could be held liable for any injuries caused by the generic product, which could result in FDA requiring additional REMS elements or taking further regulatory action against the RLD.⁸¹ In addition, adverse events associated with the generic could impact the RLD holder’s reputation.⁸² As aforementioned, FDA can review the generic product developer’s bioequivalence protocol and send a letter to the RLD holder stating that providing samples for such testing would not be a violation of the REMS; however, FDA does not have the authority to compel the RLD holder to provide the samples. The Pharmaceutical Research and Manufacturers of America (PhRMA) trade group has provided feedback to FDA on the guidance, writing that “final guidance should provide meaningful detail on how FDA plans to ensure that a [bioequivalence] study contains adequate safety measures to protect research participants.” 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 the RLD for the necessary testing.⁸³

The second issue concerns entry into a single, shared system REMS, 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 RLD and generic must enter into a single, shared system REMS. The purpose of this requirement is to reduce the burden for stakeholders (e.g., health care providers and patients) by providing a single portal to access REMS materials and

⁷⁹ 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.

⁸⁰ 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/remes-the-next-pharmaceutical-enforcement-priority.ashx>.

⁸¹ *Ibid.*

⁸² *Ibid.*

⁸³ 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)

other documentation. The FDA and generic drug industry 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.⁸⁴ 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.⁸⁵ This is consistent with an FDA presentation stating that 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.⁸⁶

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.”⁸⁷ In the 112th Congress, in response to concerns surrounding misuse of REMS, an early version of the Food and Drug Administration Safety and Innovation Act (FDASIA; P.L. 112-144) 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, among other things.⁸⁸ Section 1131 was ultimately not included in the final version of the bill signed into law as FDASIA.

In the 115th 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 2017, or the FAST Generics Act of 2017 (H.R. 2051) and the Creating and Restoring Equal Access to Equivalent Samples Act of 2017, or the CREATES Act of 2017 (S.

⁸⁴ 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>. 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>.

⁸⁵ 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>.

⁸⁶ Elaine Lippman, FDA, CDER, Office of Regulatory Policy, *Development of Shared System REMS*, <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM539368.pdf>.

⁸⁷ 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>.

⁸⁸ 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).

974, H.R. 2212).⁸⁹ The FAST Generics Act and CREATES Act use the term *covered product* to refer to any drug approved under FFDCA Section 505(b) or 505(j), a biologic licensed under PHSA Section 351, or a combination thereof “when reasonably necessary to demonstrate sameness, biosimilarity, or interchangeability,” excluding drugs and biologics that appear on the drug shortage list under FFDCA Section 506E, as specified; *eligible product developer* to refer to a person that seeks to develop a product for approval pursuant to an application for approval under FFDCA Section 505(b)(2) or 505(j), or for licensing under PHSA Section 351(k); and *license holder* to refer to the sponsor of an approved NDA, ANDA, or BLA for a covered product.⁹⁰

The FAST Generics Act of 2017 (H.R. 2051)

The FAST Generics Act seeks to generally limit a license holder of a covered product 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.

The CREATES Act of 2017 (S. 974, H.R. 2212)

The CREATES Act would likewise establish a mechanism for an eligible product developer to obtain the covered product for testing. The legislation would allow the product developer to bring a civil action against the license holder for failure to provide the eligible product developer sufficient quantities of the drug on “commercially reasonable, market-based terms.” If the eligible 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 CREATES Act would allow the Secretary to require modification to an approved REMS to accommodate different approved REMS for the RLD and generic product. It would provide the Secretary with additional flexibility to waive the requirement for a single shared system of

⁸⁹ Earlier versions of both bills were introduced in the 114th Congress: 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]).

⁹⁰ Although the term *application holder* is generally used to describe the sponsor of an approved NDA or ANDA, and the term *license holder* is used to refer to the holder of a BLA, the bills do not make this distinction.

ETASU, unless the Secretary determines that no different, comparable aspect of the ETASU would satisfy the statutory requirements. Like the FAST Generics Act, the CREATES Act also contains a limitation of liability provision.

REMS Reform and Cost-Savings

Although legislation aimed at reforming REMS has been discussed as a means of reducing health care spending, CRS is not aware of any formal cost estimates (from CBO or other entities) that indicate how the FAST Generics or the CREATES Act would function as a cost saving measure. Some entities have shared informal cost estimates.

CBO had formally scored a similar provision from the 112th Congress—Section 1131 “Drug Development and Bioequivalence Testing” of S. 2516—an early version of the FDASIA legislation.⁹¹ Section 1131 would have generally prohibited the use of ETASU to restrict availability of a covered drug for bioequivalence 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. However, it would not have addressed the issue of developing a single, shared system REMS and unlike the FAST Generics and CREATES bills, the definition of “covered drug” under Section 1131 was narrower and would have included only drugs and biologics subject to a REMS with ETASU. The FAST Generics Act and CREATES Act seek to also limit the brand manufacturer’s ability to restrict the availability of samples of drugs and biologics 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.⁹² 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

In July 2017, FDA held a public meeting and provided the public with the opportunity to comment “on the appropriate balance between encouraging innovation in drug development and accelerating the availability to the public of lower cost alternatives to innovator drugs.”⁹³ Various comments submitted to the docket have addressed the REMS issues raised in this CRS report.

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; now called the 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.⁹⁴ 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

⁹¹ A later version, S. 3187, was enacted as FDASIA (P.L. 112-144).

⁹² 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>.

⁹³ FDA, “Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access; Public Meeting,” <https://www.fda.gov/Drugs/NewsEvents/ucm563986.htm>.

⁹⁴ 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.

generic medicines.”⁹⁵ 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.”⁹⁶ 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.”⁹⁷

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⁹⁵ GPhA, Letter to Senators Grassley, Leahy, Lee, and Klobuchar, June 14, 2016, http://www.gphaonline.org/media/cms/CREATES_Act_Group_Letter.pdf.

⁹⁶ 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.

⁹⁷ 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>.