United States Government Accountability Office

Report to the Chairman, Committee on Energy and Commerce, House of Representatives

October 2019

GENERIC DRUG DEVELOPMENT

Stakeholders' Views of Risk Evaluation and Mitigation Strategies Differ

GAO-20-94

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GAO Highlights

Highlights of GAO-20-94, a report to the Chairman, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

To manage the risks posed by some drugs, FDA requires drug companies to establish risk evaluation and mitigation strategies. Companies developing generic drugs generally need samples of the reference standard drug to conduct bioequivalence testing. Generic companies may also have to negotiate a shared system with the reference drug company, when that company's drug is subject to certain REMS requirements.

FDA and FTC officials acknowledge that some drug companies have used certain practices that prevent or delay the development of generic drugs. The practices include limiting access to samples of reference standard drugs with and without REMS and delaying negotiations for creating required shared systems. GAO was asked to review drugs subject to REMS and drug companies' experience with these practices. This report describes (1) the drugs subject to REMS, and (2) FDA and FTC's efforts to address these practices, and stakeholders' views on agencies' efforts.

GAO analyzed FDA data on the conditions these drugs treat and the REMS requirements that apply to the drugs. GAO also interviewed FDA and FTC officials and representatives from five reference drug companies and four generic drug companies, which GAO selected based on a variety of factors, including the companies' experiences with drugs subject to REMS. GAO also reviewed public comments and related documents from FDA and FTC.

HHS and FTC provided technical comments on a draft of this report, which GAO incorporated as appropriate.

View GAO-20-94. For more information, contact John Dicken at (202) 512-7114 or dickenj@gao.gov

What GAO Found

The Food and Drug Administration (FDA) can require drug companies to establish risk evaluation and mitgation strategies (REMS) for drugs with serious safety concerns to ensure that a drug's benefits outweigh its risks. As of March 18, 2019, FDA approved 74 active REMS that cover 523 drugs that treat various conditions. One hundred forty-three of the drugs are reference standard drugs, which are drugs generic drug companies must use to conduct bioequivalence testing. Of these 143, 64 have at least one approved generic that is also subject to REMS. Ten of the REMS are shared systems that allow health care providers to obtain information from multiple companies on a drug's risks and satisfy other administrative requirements through one REMS system.

According to FDA and the Federal Trade Commission (FTC), drugs with and without REMS have been the subject of practices that can delay or prevent generic drug development and marketing. FDA and FTC have taken actions designed to address some of these practices. According to FDA officials, they are more limited in what actions they can take when drugs without REMS are involved. Drug company officials that GAO interviewed had different views on these actions. To address practices that may limit access to samples of reference standard drugs and keep generic drugs from the market:

- FDA issued draft guidance in 2014 on how generic companies could obtain a letter stating that the agency would not consider it a REMS violation to provide reference standard drug samples to the generic company requesting the letter. Three of the four generic companies GAO interviewed said these letters were not useful because they do not require drug companies to share samples. In contrast, officials from three of five reference drug companies said the letters addressed their safety concerns about providing samples to generic companies. FDA does not issue such letters for drugs without REMS.
- In February 2019, FDA published a list of drug companies whose reference standard drugs were the subject of access inquires made to FDA by generic drug companies. One of the four generic companies GAO spoke with said FDA's list was helpful, and one reference drug company said it was uncertain why it was included on the list.
- FTC has reviewed inquiries it received from FDA and generic companies, and has filed amicus briefs in two cases involving drugs with REMS. According to FTC, to date, the agency has not brought a case charging a drug company with violating federal antitrust law for refusing to provide samples to a generic drug company.
- To address practices that may delay negotiations between reference drug and generic drug companies for creating required shared systems, FDA issued waivers and related guidance that allowed generic companies to develop a separate, but comparable, REMS shared system. One generic drug company said the guidance on waivers was helpful; however, one drug company said the waivers put added burden on health care providers who have to use multiple REMS systems.

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Abbreviations

CMS	Centers for Medicare & Medicaid Services
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FTC	Federal Trade Commission
HHS	Department of Health and Human Services
REMS	risk evaluation and mitigation strategies

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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Washington, DC 20548

October 15, 2019

The Honorable Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

All drugs pose some level of safety risk to patients, but certain drugs have more serious risks associated with them than others, such as a risk for severe adverse events. To ensure the benefits of certain drugs outweigh their risks, the Food and Drug Administration (FDA) can require drug companies to establish risk evaluation and mitigation strategies (REMS) for these drugs.[1] For example, FDA may require drug companies to place certain conditions on a drug subject to REMS, such as who can distribute the drug and where it can be done, such as in hospitals.

In recent years, generic companies have raised concerns that some drug companies have used certain practices involving REMS requirements to hinder competition by delaying or preventing generic drugs from being developed or coming to market.[2] Drug companies have also used these practices for drugs that are not subject to REMS. Reference listed drugs, typically brand name drugs, are drugs already approved by FDA. Generic drug companies generally use samples of reference standard drugs to test whether their generic drugs are bioequivalent to the corresponding

[1]FDA's authority to require REMS was established in the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926 (2007).

[2]Generic drugs are essentially duplicates of another drug that has already been approved for marketing. Other factors can delay a generic company bringing a generic drug to market. For example, a reference drug may have patents or marketing exclusivities that prevent approval of a generic drug application. Patents or marketing exclusivities as potential barriers to the marketing of generic drugs, as patents and marketing exclusivities were not the focus of this report.

reference listed drug.[3] Once available, generic drugs can provide substantial cost savings for patients and third-party payers, including government health programs.[4]

FDA and the Federal Trade Commission (FTC) have identified two practices that could hinder generic drug companies' ability to develop generic drugs: (1) limiting generic drug companies' access to samples of reference standard drugs, which are necessary to test whether the generic drug is bioequivalent to the reference listed drug, and (2) delaying negotiations between reference drug and generic drug companies that must be completed before certain generic drugs can be marketed.[5]

You asked us to review drugs subject to REMS and the practices identified by FDA and FTC that may prevent generic drugs from coming to market. This report describes

1. the drugs subject to REMS and the requirements established by these REMS; and

[3]To be approved as a generic drug, the drug must generally be the same as the reference listed drug with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) bioequivalent to the reference listed drug, meaning it generally delivers the same amount of active ingredient(s) in the same amount of time as the reference listed drug. When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug.

[4]As we reported in 2016, generic drugs can have retail prices that are 75 to 90 percent lower, on average. GAO, *Generic Drugs Under Medicare: Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, GAO-16-706 (Washington, D.C.: Aug. 12, 2016).

[5]Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA, *Restricted Distribution Systems in the Pharmaceutical Supply Chain*, testimony before the House Committee on Oversight and Government Reform Subcommittee on Health Care, Benefits, and Administrative Rules, 115th Cong., 1st sess., March 22, 2017, and Markus H. Meier, Acting Director, Bureau of Competition, FTC, *Antitrust Concerns and the FDA Approval Process*, testimony before the House Judiciary Committee, Subcommittee on Regulatory Reform, Commercial, and Antitrust Law, 115th Cong., 1st sess., July 27, 2017. FDA, an agency within the Department of Health and Human Services (HHS), is responsible for the approval of drugs that meet safety and efficacy standards for the U.S. market. FTC is responsible for protecting consumers and competition by enforcing federal antitrust laws that prohibit anticompetitive, deceptive, and unfair business practices, and also investigates claims of anticompetitive behavior in the drug industry.

2. FDA and FTC's efforts to address practices that may hinder the development and marketing of generic drugs and what drug companies and stakeholders have said about these efforts.

To describe drugs subject to REMS and the requirements established by the REMS, we analyzed FDA data, as of March 18, 2019, on drugs for which FDA has approved REMS. To further describe drugs subject to REMS, we analyzed FDA data to identify additional characteristics of these drugs, including orphan drugs.[6] To determine the medical conditions that drugs subject to REMS are intended to treat, we identified the therapeutic classes of these drugs using RED BOOK data from March 2018, and characterized the therapeutic classes by medical conditions.[7] We also estimated Medicare Part D and Medicaid drug spending for a select number of reference standard drugs for which cost data were available. We also compared spending for a select number of reference standard drugs to spending for a corresponding generic drug. To do this, we used publicly available data from the Medicare Part D Drug Spending Dashboard and the Medicaid Drug Spending Dashboard, maintained by the Centers for Medicare & Medicaid Services (CMS).[8] These data covered drug spending and utilization for both of these programs for calendar year 2017, the most current data available at the time of our review.[9] To assess the reliability of the FDA data, we performed data checks and interviewed agency officials. To assess the reliability of the Medicare and Medicaid drug spending data, we interviewed agency

[6]Orphan drugs are those intended to treat a disease or condition that affects fewer than 200,000 people in the United States, or that affects more than 200,000 people in the United States but for which there is no reasonable expectation of recovering the cost of drug development and marketing. 21 U.S.C. § 360bb(a)(2).

[7]RED BOOK is a compendium published by Truven Health Analytics that includes information about the characteristics of drug products.

[8]The Medicare Part D Drug Spending Dashboard is an interactive, web-based tool that presents spending information for Medicare Part D drugs—drugs that patients generally administer themselves and that are paid through the Medicare Part D program (which represents approximately 70 percent of Medicare beneficiaries). The Medicaid Drug Spending Dashboard is another interactive, web-based tool that presents spending information for drugs paid through the Medicaid program. Medicaid drug data represent national-level drug utilization data for covered outpatient drugs paid for by state Medicaid agencies.

[9]Not all spending data for Medicare and Medicaid were included in the data. For example, drugs with fewer than 50 Medicare or Medicaid claims in 2017 were excluded from their respective data. Also, some reference listed drugs subject to REMS were approved after 2017 and, thus, would not appear in CMS's spending data.

officials. We determined that these data were sufficiently reliable for the purposes of our reporting objective.

To identify FDA's and FTC's efforts to address practices that could hinder the development and marketing of generic drugs and what drug companies and other stakeholders have said about these agencies' efforts, we interviewed FDA and FTC officials and reviewed agency documents, such as guidance documents, about their efforts. We interviewed officials from two stakeholders representing drug companies. We also interviewed officials from nine drug companies who have experience with drugs subject to REMS about these agencies' efforts.[10] We used the following three criteria to identify a range of generic drug companies with whom to speak: (1) whether they made six or more inquiries to FDA regarding their inability to access samples of reference standard drugs; (2) whether they had experience negotiating a required shared system (a system implemented jointly by two or more drug companies to coordinate certain REMS activities, which is required for some generic drugs); and (3) the different medical conditions their drugs were intended to treat in order to obtain a range of drugs. After applying our criteria, we selected four generic drug companies. To obtain the reference drug companies' perspectives, we selected five drug companies whose reference standard drugs were the subject of sample access inquiries from the four generic companies that we selected. We asked these drug companies about their opinions on FDA and FTC's efforts to address these specific practices. To supplement our interviews with stakeholders and drug companies, we reviewed 16 comments to the Federal Register related to FDA's efforts.[11] We selected these 16 comments out of a total of 42 comments because they were submitted by stakeholders representing professional associations, patient advocacy groups, and drug companies. These comments included two additional drug companies beyond those we interviewed as well as organizations representing professional associations, such as pharmacists. We also excluded comments submitted by individuals.

[10]FDA, *Restricted Distribution Systems in the Pharmaceutical Supply Chain*, testimony before the House Committee on Oversight and Government Reform Subcommittee on Health Care, Benefits, and Administrative Rules, March 22, 2017 and FTC, *Antitrust Concerns and the FDA Approval Process*, testimony before the House Judiciary Committee, Subcommittee on Regulatory Reform, Commercial, and Antitrust Law, July 27, 2017.

[11]79 Fed. Reg. 72,185 (Dec. 5, 2014); 83 Fed. Reg. 25,465 (June 1, 2018); 83 Fed. Reg. 44,273 (Aug. 30, 2018).

We conducted this performance audit from March 2018 through October 2019 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

FDA approves reference listed drugs and generic drugs that meet safety and efficacy standards for marketing in the United States.[12] Generic drug companies must show that their drug is (1) the same as the reference listed drug with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences, as approved by FDA); and (2) bioequivalent to the reference listed drug, meaning it generally delivers the same amount of active ingredient(s) in the same amount of time as the reference listed drug.[13]

When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug.

REMS

All drugs pose some level of safety risk to patients. According to FDA, for most drugs, routine, risk-minimization measures, such as FDA-approved professional labeling, are sufficient to protect the public from the drug's risks.[14] However, in some cases, FDA may require a drug company to take additional actions to ensure that the benefits of the drug outweigh its

[12]Generally, the approval of a reference listed drug is based on FDA's review and approval of a new drug application containing data on the safety and effectiveness of the drug as determined through clinical trials or other research. See 21 U.S.C. § 355(b). The approval of a generic drug is based on FDA's review and approval of an abbreviated new drug application. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. See 21 U.S.C. § 355(j).

[13]See 21 U.S.C. § 355(j)(2)(A) & (4).

[14]According to FDA, such professional labeling describes the conditions in which the drug can be used safely and effectively and is updated periodically to incorporate information from surveillance once the drug has been on the market, or from studies revealing new benefits (e.g., new indications or formulations) or risks.

risks and to help mitigate or prevent serious risks of adverse side effects. Specifically, FDA may require the drug company to establish a REMS that includes one or more risk-mitigation strategies beyond the drug's professional labeling.

According to FDA, most REMS are designed to reinforce patients' and health care providers' behaviors and actions that support the safe use of the particular drug they cover. For example, FDA may require drug companies to give patients and health care providers additional information to reinforce certain safe use conditions or specific risks described in the approved labeling of a certain drug. FDA may require a REMS either before a drug is approved or after approval if FDA becomes aware of new safety information. When determining whether a REMS is necessary, FDA considers several factors, including, for example, the estimated size of the population likely to use the drug and the seriousness of the disease or condition being treated.

FDA may require a REMS to include one or more components. For example, FDA may require drug companies to provide patients with certain information in the form of medication guides.[15] Generally, medication guides include information on serious side effects, including those that might require emergency medical care or involve life-threatening conditions. Similarly, FDA may require drug companies to develop communication plans for how the drug company will disseminate information to health care providers. Communication plans can include, for example, information on any serious risks of the drug and any safety protocols to ensure its safe use. Thus, for one REMS, FDA could require a drug company to provide a medication guide. For a second REMS, FDA could require a drug company to provide both a medication guide and a communication plan. Table 1 below includes a list of selected REMS

[15]FDA may also require drug companies to provide patients with information in the form of patient package inserts. Patient package inserts are required for oral contraceptives or estrogen-containing drugs and includes information on how to take the drug, and when applicable, the effectiveness of oral contraceptives.

components.[16] Additionally, if a reference listed drug is subject to a REMS, an approved generic drug is also subject to some of the same REMS requirements.[17]

[16]In addition to those described above, there are two other REMS components that FDA can require. The first is a timetable for the submission of REMS assessments, which the drug company must provide to FDA by certain dates after approval of the REMS. This component is required for all REMS, so we do not report on it. The second involves packaging or disposal technology. For this component, drug companies are required to make their drugs available in packaging that mitigates serious risk of abuse, such as in unit dose packaging, or with a safe disposal system for purposes of rendering the drug unavailable and unusable for all practical purposes. We do not report on this component because, at the time of our data analysis (March 18, 2019), FDA had not imposed any REMS with this component.

[17]A generic drug is subject to only the following REMS components that are required for a reference listed drug: (1) medication guide or patient package insert, (2) packaging or disposal technology, and (3) specific safe-use measures, called "elements to assure safe use" (ETASU). See 21 U.S.C. § 355-1(i)(1).

Table 1: Selected REMS Components Required by FDA

Selected REMS component	Description
Medication guide[a]	Information on a drug's risks that is targeted toward patients. Written in nontechnical language and provided when the drug is dispensed to the patient.
Communication plan	Information on a drug's risks that is targeted toward health care providers, such as information to explain certain safety measures associated with a particular drug.
Elements to assure safe use (ETASU)	Required actions that must be taken before a drug can be prescribed, dispensed, or received. Intended for drugs that can be marketed only if there are requirements in place to mitigate a specific serious risk listed in the drug's labeling. Can involve additional requirements for the drug company: • Implementation system—A system to enable the drug company to monitor and evaluate implementation of the ETASU measures by health care providers, pharmacists, and other responsible parties. Required by FDA for certain ETASU measures. • Required shared system—A system used by multiple drug companies to coordinate their REMS activities and information about a drug's risks. Required by FDA if a reference listed drug is subject to a REMS with ETASU and a generic version is being developed.

Source: GAO summary of the Federal Food, Drug, and Cosmetic Act § 505-1. | GAO-20-94

Note: Risk evaluation and mitigation strategies (REMS) are safety programs the Food and Drug Administration (FDA) can require for certain drugs with serious safety concerns to ensure that the benefits of a drug outweigh the risks. In addition to those described above, there are two other REMS components that FDA can require. The first is a timetable for the submission of REMS assessments, which the drug company must provide to FDA by certain dates after approval of the REMS. This component is required for all REMS. The second involves packaging or disposal technology. For this component, drug companies are required to make their drugs available in packaging that mitigates serious risk of overdose or abuse, such as unit dose packaging, or with a safe disposal system for purposes of rendering the drug unavailable and unusable for all practical purposes.

[a]FDA may also require drug companies to provide patients with information in the form of patient package inserts. Patient package inserts are required for oral contraceptives or estrogen-containing drugs and includes information on how to take the drug, and when applicable, the effectiveness of oral contraceptives.

FDA can also require drug companies to implement another REMS component, called "elements to assure safe use" (ETASU), if a drug has been shown to be effective, but is associated with a specific serious risk. Depending on the risk, FDA may require any or all of the following ETASU measures:

- Prescribers have specific training or special certifications;
- Pharmacies or health care settings where the drug is dispensed have special certification;
- Drugs are dispensed only in certain health care settings, such as hospitals;

- Drugs are dispensed with evidence of safe-use by the patient, such as requiring a patient's acknowledgement that she has been counseled on a drug's risks and understands and accepts these risks;
- Patients are monitored, for example, while taking the drug for specific adverse events or outcomes; or
- Patients are enrolled in a registry for collection of certain information, such as patient outcomes and adverse reactions associated with the drug.

According to FDA, these measures are for drugs that can be marketed only if there are requirements in place to mitigate a specific serious risk listed in the drug's labeling. If FDA requires certain ETASU measures, it may also require a drug company to develop an implementation system to enable the drug company to monitor and evaluate implementation of the ETASU measures by health care providers, pharmacists, and other responsible parties.

Also, if a reference listed drug is subject to a REMS with ETASU and a generic version is being developed, the reference drug company and the generic drug company are required to develop a shared system—a system that is used by participating companies to coordinate their REMS activities and information about a drug's risks.[18] Under a required shared system, the generic drug company and the reference drug company use the same REMS documentation and other materials on the drug's risks and generally share in the implementation and maintenance of any database and infrastructure (e.g., call center). According to FDA, shared systems can be beneficial in reducing the burden for patients and health care providers, such as prescribers and pharmacies, when accessing REMS informational materials or completing administrative requirements, including any required training or certifications for providers.

Generic drug companies must submit REMS documentation and materials as part of their generic drug application. Generally, before FDA can approve generic drugs that are subject to REMS with ETASU,

[18]See 21 U.S.C. § 355-1(i)(1)(C). FDA uses the term "single shared system" to refer to a required shared system. According to FDA, it may also recommend that drug companies whose drugs have the same active ingredient or belong to the same class of products voluntarily develop and implement a shared system. For example, if two new drugs have similar risks and REMS requirements, the two new drug applicants can voluntarily form a shared system at the agency's recommendation. We refer to this as a voluntary shared system.

reference drug companies and generic companies must reach agreement on a required shared system. According to FDA, generic drug companies that are developing a required shared system should submit their proposed REMS materials to FDA by the midpoint of the application review process or another time as specified by the agency.[19] Any delays in the development of a required shared system can affect FDA's ability to approve a generic drug application. A generic company may request a waiver from FDA, which if granted, would allow the generic company to develop a separate system that includes the same ETASU measures required for the reference listed drug.[20] For example, if the reference listed drug's ETASU measures require prescriber certification and the dispensing of the drug in certain health care settings, then the generic drug company's separate system must also include the same ETASU measures.[21]

[19]FDA, *Development of a Shared System REMS, Guidance for Industry, Draft Guidance* (Silver Spring, Md.: June 2018). In its Commitment Letter for the Generic Drug User Fee Amendments of 2017, FDA stated that, for generic drug applications in the first review cycle, it would review and act on at least 90 percent of them within specified time frames—8 months for certain priority applications and 10 months for all other applications. See FDA Reauthorization Act of 2017, Pub. L. No. 115-52, tit. III, 131 Stat. 1005 (2017). See also FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*.

According to FDA, the time frame for submitting REMS materials for a shared system is at the midpoint of the application review process for a single generic drug application. If there are multiple generic drug applications, FDA may provide another time frame that aligns with the midpoint of the first application submitted.

[20]FDA may issue a waiver if, (1) the burden of forming a required shared system outweighs the benefits of having such a system, taking into account the impact on health care providers, patients, the generic drug company, and the reference listed drug company, or (2) an aspect of the ETASU is covered by an unexpired patent or entitled to trade secret protection, and the generic company was unsuccessful in obtaining a license for use. 21 U.S.C. § 355-1(i)(1)(C). See also FDA, *Waivers of the Single, Shared System REMS Requirement, Guidance for Industry, Draft Guidance* (Silver Spring, Md.: June 2018).

[21]According to FDA, although the generic company must meet the same safety level for the ETASU measures as those applied to the reference listed drug, the generic company can do so using different procedures or methods.

Practices Identified by FDA and FTC that May Hinder Generic Drug Development and Marketing

In recent years, FDA and FTC have identified two practices that can hinder competition by preventing or delaying the development and marketing of generic drugs.[22] The first practice the agencies identified involves limiting access to samples of reference standard drugs, which generic companies generally need to conduct bioequivalence testing. This practice can apply both to reference standard drugs subject to REMS, specifically those subject to certain ETASU measures, and those not subject to REMS.[23] For example, some drug companies might limit access to samples of reference standard drugs subject to REMS, citing ETASU measures that limit distribution, such as the measure that limits distribution of drugs subject to REMS to only certain health care settings.[24] Additionally, drug companies may limit access to samples of reference standard drugs that are not subject to REMS. Typically, generic companies obtain samples through normal distribution channels such as wholesale distributors. However, drug companies could, for example, limit the sale of their reference standard drugs to certain pharmacies, such as specialty pharmacies.[25] FDA and FTC have testified before Congress that these distribution limits—for reference standard drugs with and without ETASU-related distribution measures—can hinder generic companies' ability to develop generic drugs and to submit a generic drug application to FDA for review.[26]

[22]Other factors can delay when a generic drug company can bring a generic drug to market. For example, a reference listed drug may have patents or marketing exclusivities that prevent approval of a generic drug application. We do not discuss patents or marketing exclusivities as a potential barrier to the marketing of generic drugs, as patents and marketing exclusivities were beyond the scope of this report.

[23]An example of an ETASU-related limited distribution measure would be when drugs are provided only to patients with prescriptions from specially certified physicians or in pharmacies under specified conditions.

[24]Federal law prohibits any reference drug company whose drug is subject to a REMS with ETASU from using an aspect of the REMS to "block or delay approval" of a generic drug application. 21 U.S.C. § 355-1(f)(8).

[25]Specialty pharmacies handle activities, such as the distribution of particular drugs, for patients with rare or chronic diseases. These pharmacies handle drugs that tend to be more difficult to administer, store, and monitor than traditional drugs.

[26]FDA, *Restricted Distribution Systems in the Pharmaceutical Supply Chain*, testimony before the House Committee on Oversight and Government Reform Subcommittee on Health Care, Benefits, and Administrative Rules, March 22, 2017, and FTC, *Antitrust Concerns and the FDA Approval Process*, testimony before the House Judiciary Committee, Subcommittee on Regulatory Reform, Commercial, and Antitrust Law, July 27, 2017.

The second practice involves circumstances when a reference drug company delays its negotiations with generic drug companies on a required shared system. The negotiations to develop a required shared system can be complex because all parties must agree on the implementation of the REMS as well as issues related to cost-sharing, confidentiality, and product liability concerns. As part of their generic drug application, generic companies must include an adequate REMS program in order to be approved. Therefore, delays in the development of a required shared system can affect FDA's ability to approve a generic drug application.

Drugs Subject to REMS Vary in the Risks They Pose, Treat a Variety of Conditions, and About Half of Approved REMS Place Limits on Distribution

Drugs Subject to REMS Vary in Risks, Treat a Variety of Conditions, and Accounted for at Least $11 Billion in Federal Spending

Our analysis of FDA data shows that as of March 18, 2019, there were 74 approved active REMS that apply to 523 drugs.[27] These drugs pose a variety of risks to users, treat a variety of conditions, and some are generics. A REMS can apply to one drug, more than one drug, or to a large number of drugs. Specifically, the approved REMS apply to:

- 136 drugs because they pose a high risk of serious medical side effects,

[27]During the time frame for our analysis, there were 523 applications that were subject to REMS. For the purposes of this report, we consider the 523 applications to be 523 drugs. The 523 drugs subject to REMS includes reference listed drugs, generic drugs, and drugs that have been discontinued. At least 48 of the 523 drugs subject to REMS have been discontinued. According to FDA, drugs that are discontinued have either never been marketed, have been discontinued from marketing, are for military use, are for export only, or have had their approvals withdrawn for reasons other than safety or efficacy after being discontinued from marketing.

According to FDA officials, as of March 18, 2019, FDA had approved a total of 276 REMS, but only 74 REMS are active.

- 384 drugs because they pose a high risk of serious medical side effects from misuse and abuse, and
- Three drugs because they have the risk of medical side effects from both the use of the drug and from misuse and abuse.

These drugs also treat at least 15 different types of medical conditions such as cancer, cardiovascular, and respiratory conditions. Twenty-two are orphan drugs, which are drugs intended to treat rare diseases.[28] One hundred forty-three of these drugs are reference standard drugs, and 64 of these reference standard drugs have one or more approved generics that are also subject to REMS.[29] (See Table 2) For example, FDA approved a generic of the drug Clozaril, which is used to treat mental and mood disorders. Both Clozaril and its generic, Clozapine, are subject to a REMS to prevent adverse medical side effects.

[28]Orphan drugs are those intended to treat rare diseases or conditions that affect fewer than 200,000 people in the United States, or that affect more than 200,000 people in the United States but for which there is no reasonable expectation of recovering the cost of drug development and marketing. 21 U.S.C. § 360bb(a)(2). For example, one of these drugs, Pomalyst is subject to REMS in order to mitigate the risk of embryo-fetal exposure. FDA gave Pomalyst orphan drug status because it is intended to treat multiple myeloma, a rare cancer that is diagnosed in 21,700 patients in the United States each year.

[29]Reference standard drugs are the products generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is available, it is also designated as the reference standard drug. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug.

Table 2: Medical Conditions Treated by Drugs Subject to Risk Evaluation and Mitigation Strategies (REMS)

	Number of drugs by medical condition	
Type of medical condition	**Reference standard drugs[a]**	**Generic drugs**
Viral	1	4
Blood disorders	3	0
Cancer	11	0
Cardiovascular/respiratory	8	0
Connective tissue	1	0
Dermatologic	2	5
Gastrointestinal	3	4
Hormonal	10	9
Immunological	6	33
Kidney and dialysis	2	0
Mental and mood disorders	6	10
Metabolic disorders	2	0
Multiple Sclerosis and central nervous system	6	7
Obesity and weight loss	1	0
Pain and opioid dependence	81	300
Total	**143**	**372**

Source: GAO's analysis of FDA data. | GAO-20-94

Note: REMS are drug safety programs that FDA can require for certain drugs with serious safety concerns to ensure the benefits of the drug outweigh the risks. The total number of reference standard drugs (143) and generic drugs (372) do not sum to 523 drugs. In eight cases, a REMS that applied to one drug could not be categorized as a reference standard drug or a generic drug. Thus, we removed these eight drugs from our analysis.

[a]Reference standard drugs are the products generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is available, it is also designated as the reference standard drug. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug.

Medicare and Medicaid paid at least $11.8 billion in 2017 for reference standard drugs subject to REMS. Specifically, in 2017 Medicare paid at least $8.5 billion for 83 of 139 reference standard drugs subject to REMS.[30] This amount accounted for at least 8 percent of all Medicare

[30]Of the 143 reference standard drugs subject to REMS in our analysis, we identified four with duplicate cost data. We excluded these four duplicates, resulting in 139 reference standard drugs subject to REMS used in our analysis of Medicare and Medicaid drug spending.

drug spending in 2017.[31] In the same year, Medicaid paid at least $3.3 billion—or at least 15 percent of all Medicaid drug spending—for 83 of the 139 reference standard drugs subject to REMS.[32] Appendix I provides information from available data on Medicare and Medicaid spending on reference standard drugs subject to REMS.

Almost Half of FDA's 74 Active REMS Include Limits on How Drugs Are Distributed, and 10 Established a Shared System

Of the 74 active REMS in our analysis, 51 have at least one required ETASU measure, and 35 specifically limit how drugs are distributed. Thirty-one of the 74 active REMS also require medication guides explaining the risks of the drug to be given to patients, and 12 require a communication plan for how the company will disseminate information to health care providers. Similar to how the 74 active REMS can have more than one REMS component, the 51 active REMS with ETASU measures can have more than one required measure. For example, 19 active REMS have an ETASU measure requiring patients to be enrolled in a registry and an ETASU measure requiring drug companies to provide training to prescribers of the drugs.

Over half of the 51 active REMS with ETASU include measures that may limit how drugs are distributed. Specifically, 35 active REMS with ETASU measures include a requirement for drug companies to ensure drug dispensing settings are specially certified before they distribute the drugs.[33] The certification process may require dispensing pharmacies to enroll in education programs provided by the drug companies. For example, to mitigate the risk of accidental overdoses from the misuse and abuse of fentanyl products, dispensing pharmacies are required to

[31]Part D is Medicare's voluntary prescription drug benefit. Private companies, known as Part D plan sponsors, contract with CMS to provide drug coverage to Medicare beneficiaries. Price concessions are payments that are negotiated between the private insurance companies and drug manufacturers to reduce the private insurance companies' drug costs. Rebates from drug manufacturers are the most common type of price concessions.

Overall, Medicare accounted for approximately $101 billion in spending for retail prescription drugs in 2017. CMS, National Health Expenditure Accounts 2017, Table 4. The amount Medicare Part D paid on reference standard drugs subject to REMS in 2017 includes amounts that Medicare Part D drug plans paid and beneficiaries' Part D payments, such as copays, but not price concessions, such as manufacturer rebates.

[32]Medicaid spent approximately $21.3 billion for drugs in 2017. CMS, National Health Expenditure Accounts 2017, Table 19.

[33]There are other ETASU measures related to distribution, however according to FDA, data for these measures are not readily available.

complete an education program that addresses—among other things—the risks of fentanyl products, patient selection, drug dosage, and patient counseling.

In addition, for 10 of the 74 active REMS, companies have entered into a shared system.[34] In three of the 10 shared systems, generic companies received a waiver from the shared system requirement after they were not successful in negotiating a shared system with the reference drug companies. In these three cases, the generic drug companies entered into shared systems that are separate from the reference drug company systems.[35] For example, after developing generics of Lotronex, which is subject to REMS with ETASU and intended to treat gastrointestinal conditions, the generic companies were required to enter into a shared system with the reference drug company. When these companies were not successful in negotiating a required shared system, FDA determined the burden of developing a required shared system with the reference drug company outweighed the benefits of having one and waived the requirement. Once FDA granted the waiver, multiple generic companies were allowed to share REMS materials and administrative requirements with heath care providers via one shared system that is separate from Lotronex's REMS system.

[34]If a reference listed drug is subject to a REMS with ETASU, the reference drug company and any generic drug company developing a generic version of the reference listed drug are required to enter into a shared system. 21 U.S.C. § 355-1(i)(1)(C). According to FDA, it may also recommend that drug companies whose drugs have the same active ingredient or belong to the same class of products voluntarily develop and implement a shared system. It is unclear from FDA data which of these 10 systems are required shared systems and which are voluntary shared systems. Since conducting our analysis on March 18, 2019, four additional shared systems were approved by FDA.

[35]To assure that the required shared system waiver does not unduly burden the health care system, FDA has only granted waivers where the generic drug applicant agrees to share its REMS system with any concurrent or subsequent applicants.

FDA and FTC Have Taken Actions to Address Practices They Identified; Drug Companies and Stakeholders Disagreed on the Usefulness of the Actions

FDA and FTC Have Taken Actions to Facilitate Access to Samples of Reference Standard Drugs and Required Shared Systems Negotiations

FDA and FTC have taken four actions to address circumstances when generic drug companies cannot access samples of reference standard drugs or experience delays in negotiating required shared systems. According to FDA and FTC, both circumstances can hinder generic drug companies' ability to develop and market generic drugs. Three of the actions focus on making samples of reference standard drugs accessible and the fourth focuses on facilitating the development of a required shared system. While all four of the actions pertain to drugs subject to REMS, only two of the actions pertain to drugs both subject to REMS and not subject to REMS. According to FDA officials, the agency is even more limited in what actions it can take when drugs not subject to REMS are involved.

Drug Companies' Perspectives on Limited Access to Samples of Reference Standard Drugs with Elements to Assure Safe Use (ETASU) that Limit Distribution

Officials from all four of the generic drug companies we interviewed told us that their inability to access samples of reference standard drugs with ETASU measures that limit distribution either delayed or discouraged them from developing generic drugs.

Officials from two of the five reference drug companies we interviewed told us they were unaware of specific instances when generic companies had difficulty obtaining samples or that generic companies had requested samples of reference standard drugs with ETASU measures that limit distribution. Also, officials from two reference drug companies cited safety concerns as the reason for limiting the distribution of their drug.

Source: GAO analysis of interviews with drug companies. | GAO-20-94

- **FDA issued draft guidance on how to obtain a safety determination letter.** One of FDA's actions focused on facilitating generic drug companies' access to reference standard drugs with ETASU-related limited distribution measures. (See sidebar for drug companies' perspectives on this practice.) In 2014, FDA issued draft guidance describing how a generic drug company could ask the agency to send what is known as a safety determination letter to the reference drug company on the generic drug company's behalf.[36] The draft guidance explains how FDA could send a letter stating that the agency had reviewed the generic company's plans for its bioequivalence testing and determined that these plans included safety measures that were comparable to those in the ETASU measures for the reference standard drug. For example, if the reference standard drug's ETASU required protections to prevent fetal exposure to the drug, the generic company's plans should include the same protections. The safety letter would also note that FDA would not consider it a REMS violation to provide reference standard drug samples to the generic company requesting the safety determination letter. According to FDA, some reference drug companies were concerned that providing samples to the generic drug company would violate REMS requirements.

  From 2016 to 2018, FDA issued 12 safety determination letters to reference drug companies on behalf of generic companies, according to agency data. However, FDA did not issue a safety determination letter for all of the requests it received.[37] According to FDA officials, there are various reasons why they might not issue a safety determination letter to the reference drug company. For example, a generic company must sign a disclosure form in order for FDA to send the letter to the reference drug company, but the generic company

[36]FDA, *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD, Guidance for Industry, Draft Guidance* (Silver Spring, Md.: Dec. 2014).

[37]During this same time frame, FDA received 22 requests. According to FDA officials, requests for a safety determination letters and the issuance of a safety determination letter may occur in different years. For example, a request may be received in 2016, but not issued until 2017.

does not always choose to do this.[38] Additionally, the generic company might have withdrawn its request for a safety determination letter, or FDA might be waiting for additional information from the generic company in order to complete its review. According to FDA officials, there is no need for a safety determination letter (which assures the reference drug company that providing samples to the generic drug company will not be considered a violation of their REMS) when there is no REMS for the product in the first place.

- **FDA published a web page with information about inquiries that included drugs both subject to and not subject REMS.** In February 2019, FDA published a web page with information on inquiries made to FDA by generic companies seeking to obtain samples of reference standard drugs in order to develop generic drugs.[39] (See sidebar for drug companies' perspectives on this practice.) FDA officials said they published this list to increase transparency about continuing issues related to accessing samples and to raise awareness about the potential effect these issues might have on reducing competition in the drug market. This list included drugs subject to and not subject to REMS, the names of reference drug companies, and the number of inquiries made. According to the web page as of February 2019, inquiries were made for 54 reference standard drugs, including 25 drugs with ETASU-related limited distribution measures and 29 drugs without such measures.[40] According to FDA data, the number of inquiries had been generally decreasing in the years prior to when the list was published.[41]

Drug Companies' Perspectives on Limited Access to Samples of Reference Standard Drugs Not Subject to Risk Evaluation and Mitigation Strategies (REMS)

Officials from three of the four generic companies in our review told us they had experience with drug companies' imposed distribution limits on reference standard drugs not subject to REMS. Of the four generic companies in our review, officials from one company said they were not able to obtain the samples they needed and chose not to pursue developing a particular drug.

Officials from one of the five reference drug companies said they have limited distribution for reference standard drugs not subject to REMS. They said their companies do so to ensure that their products are efficiently distributed, in part by using certain pharmacies.

Source: GAO analysis of interviews with drug companies. | GAO-20-94

[38]Once FDA has reviewed submitted bioequivalence study protocols and determined that they contain safety precautions comparable to those in the applicable REMS for the reference standard drug, FDA will notify the generic company of the determination by letter. The generic company can then request that FDA send a separate letter to the reference drug company stating that FDA will not consider providing samples of the drug to the generic company to be a violation of the REMS. A generic company must then authorize the disclosure of any information to the reference drug company before FDA will send a safety determination letter.

[39]This web page was an update to original information published in May 2018.

[40]According to FDA, one of the reference standard drugs on the web page was subject to access inquiries before and after its REMS ETASU measures was removed.

[41]According to FDA, after the publication of the 2014 draft guidance that describes how a generic company can request FDA to send a safety determination letter to a reference drug company, there was an increase in the number of inquiries for accessing reference drug samples. However, the numbers of these inquiries received by the agency has since returned to pre-guidance patterns.

FTC officials reviewed inquiries the agency received from FDA and generic companies and filed two briefs. FTC told us it reviewed inquiries the agency had received from generic companies and FDA, including those related to information on FDA's published web page. However, FTC officials said, to date, they have not brought a case charging a reference drug company with violating federal antitrust law for refusing to provide samples to a generic drug company. In order to take enforcement action, FTC needs to find sufficient evidence of activity that violates the Federal Trade Commission Act or the Sherman Act.[42] For example, FTC would need to find that a reference drug company's practice constituted monopolization in violation of the Sherman Act. According to FTC officials, they have not brought any antitrust cases to the courts, but have filed two amicus briefs related to cases involving drugs subject to REMS.[43] In both of these briefs, FTC noted that the generic companies' respective allegations, if true, established an antitrust violation and that the generic companies' lawsuits should be allowed to continue.

[42]The Federal Trade Commission Act, enforced by FTC, bans unfair methods of competition and unfair or deceptive acts or practices. See 15 U.S.C. §§ 41-58. The Sherman Act prohibits agreements that unreasonably restrain competition as well as monopolization, attempted monopolization, and conspiracies to monopolize. 15 U.S.C. § 1-2. Although the Department of Justice, and not FTC, enforces the Sherman Act, the Supreme Court has held that violations of the Sherman Act also violate the Federal Trade Commission Act. Therefore, FTC can bring cases under the Federal Trade Commission Act against the same kinds of activities that violate the Sherman Act. See Federal Trade Commission v. Cement Institute, 333 U.S. 683, 691-92 (1948).

[43]An amicus brief is a brief filed by an individual or entity that is not a party to a lawsuit but that has an interest or expertise in the subject matter being litigated. Brief for Federal Trade Commission as Amicus Curiae, Actelion Pharmaceuticals Ltd. v. Apotex Inc., No. 12-cv-05743, 2013 WL 5524078 (D.N.J. Sept. 6, 2013). Brief for Federal Trade Commission as Amicus Curiae, Mylan Pharmaceuticals, Inc. v. Celgene Corporation, No. 14-2094, 2016 WL 2943813 (D.N.J. June 20, 2016).

Drug Companies' Perspectives on Negotiating Required Shared Systems

Officials from one generic company said that the respective reference drug companies would not meet with them to negotiate the development of a required shared system REMS. Officials from another generic company said the negotiation process with the reference drug company lasted almost 2 years.

Officials from four of the five reference drug companies we interviewed had experience negotiating required shared systems. Officials from three of these four companies told us that developing a shared system is a difficult, challenging, and complex process. Officials from one reference drug company said that the level of complexity can increase based on the number of companies and the different people involved.

Source: GAO analysis of interviews with drug companies. | GAO-20-94

- **FDA issued waivers that allowed generic drug companies to develop a separate system from the REMS of the reference listed drug and issued draft guidance on how to obtain such a waiver.** According to FDA, since 2007, the agency has received 13 requests for a waiver from the shared system requirement, and at the time of our data collection and analysis, FDA had approved three, the first in 2013. (See sidebar for drug companies' perspective on required shared systems.) These waivers allowed the generic drug company to develop a separate system that includes the same ETASU measures required for the reference listed drug. According to officials, FDA was unable to grant the remaining waivers for different reasons. For example, the agency may still be reviewing the generic drug application submitted by the company that requested a waiver. Officials explained that the waiver request is part of the overall generic drug application and the agency cannot approve a waiver without approving the application as well. To further facilitate the process, in 2018, FDA issued draft guidance describing what factors the agency considers when granting waivers.[44] The statute authorizes FDA to grant a waiver (1) if the burden of creating a required shared system outweighs the benefit of having it, taking into account the impact on the health care providers, patients, and drug companies involved or (2) if an aspect of the ETASU is covered by an unexpired patent or entitled to trade secret protection, and the generic company was unsuccessful in obtaining a license for use.[45] FDA's guidance describes examples of the potential benefits of having a shared system and the burdens of forming a shared system on health care providers, patients and drug companies that FDA will consider. For example, having a shared system could benefit drug companies by making a REMS for multiple products more efficient. In contrast, the drug companies negotiating a required shared system could be market competitors and involved in patent litigation related to the drug product.

[44]FDA, *Waivers of the Single, Shared System REMS Requirement, Guidance for Industry, Draft Guidance* (Silver Spring, Md.: June 2018).

[45]21 U.S.C. § 355-1(i)(1)(C).

Selected Drug Companies Had Differing Views on the Usefulness of FDA's and FTC's Efforts

In general, the four generic drug companies and five reference drug companies we interviewed disagreed on the usefulness of FDA's and FTC's efforts to address the practices that may affect the development of generic drugs.

- **FDA's safety determination letters.** Officials from three of the generic companies in our review said that the safety determination letters were not useful because they were not enforceable and did not require a reference drug company to provide a generic company with samples of a reference standard drug. In its comments on FDA's draft guidance on obtaining a safety determination letter, one stakeholder representing generic companies expressed concern that reference drug companies now use safety determination letters as another requirement to obtain samples.

  In contrast, officials from three reference drug companies we interviewed told us that FDA's safety determination letters addressed their safety concerns regarding sharing samples of reference standard drugs with generic companies. Further, officials from two of these three reference drug companies said they request these letters from generic companies that request samples of reference standard drugs. Officials from the remaining two reference drug companies we interviewed said they were not aware of FDA's safety determination letters or did not have concerns or a position on the issue.

- **FDA's publication of its web page.** Officials from one of the four generic companies we interviewed told us they thought the inquiries web page published by FDA was helpful. However, this same company said it had not noticed a significant effect in being able to access samples of reference standard drugs because of the web page. Officials from another generic company said it was too early to tell about the usefulness of FDA's web page. Of the remaining two generic companies, officials from one company were unaware of the web page and officials from the second company noted that they were uncertain why a generic company would be included in the list of companies on FDA's web page.[46]

  Officials from two of the five reference drug companies we interviewed, and whose companies appeared on the web page, said

[46]As previously noted, typically the reference listed drug, or brand name drug, is the reference standard drug. However, there may be instances, such as when the reference listed drug is not available, where an approved generic drug is selected by FDA to serve as the reference standard drug for bioequivalence testing purposes.

they were unaware of any inquiries made to their companies requesting samples of reference standard drugs. Additionally, officials from one company told us they did not know why they were on FDA's published web page because the company had sold the reference standard drug to another company and had informed FDA that this had occurred.

According to FDA, the web page reflects the owner of the reference standard drug at the time the agency received an inquiry, regardless of whether the drug was later sold. Additionally, some generic companies might contact FDA directly without contacting the reference drug company because they anticipate having difficulties accessing samples of the reference standard drug. FDA notes on its web page that the agency did not independently investigate or confirm the access limitations described in the inquiries it received.

- **FTC's filing of amicus briefs.** Officials from two of the generic companies in our review said FTC's filing of amicus briefs was generally a positive step. Officials from two companies said the amicus briefs helped negotiations with reference drug companies. A third generic company said the amicus briefs helped raise awareness about issues generic companies are having. Officials from a fourth generic company said FTC's actions could impact the company's efforts to develop generic versions of reference listed drugs in the future. Officials from the five reference drug companies we interviewed did not have any comments on FTC's specific amicus briefs.
- **Waivers for a required shared system.** Officials from three of the four generic companies we spoke with had experience with waivers. Officials from one of these three companies said the waiver guidance was helpful. However, officials from this generic company and a second company said it took FDA almost a year to grant their waivers. According to officials from a third company, they obtained their waiver within a month, in part, because negotiations had been ongoing for more than a year. According to FDA officials, the review of a waiver request is part of the generic drug company's drug application. FDA will not grant a waiver unless the generic drug company meets the waiver requirements and its generic drug application is approved.

  Reference drug companies and other stakeholders expressed concerns about these waivers. Officials from three of the five reference drug companies we spoke with said the burden on health care providers or patients should be considered when granting waivers. Officials from one company specifically expressed concerns

that as FDA grants additional waivers, it could place an additional burden on the health care system. For example, health care providers could be required to use multiple systems to access REMS information on the drug's risks or to complete administrative requirements, such as required certification. The remaining reference drug companies did not have comments on the topic.

In comments we reviewed on FDA's draft guidance on these waivers, stakeholders noted concerns similar to those raised by the reference drug companies. For example, two groups representing pharmacists and pharmacies said that if FDA grants additional waivers, it could place a burden on the health care system. Historically, FDA has attempted to limit the number of required shared systems created under waivers. If a generic drug company is granted a waiver, it is allowed to create a separate system that includes the same ETASU measures required of the reference listed drug. However, to date, FDA has only granted waivers to generic drug companies that agree to share their systems with other drug companies that concurrently or subsequently develop generic or brand versions of the same reference listed drugs.

Agency Comments

We provided a draft of this product to FDA and FTC for their review and comment. Both agencies provided technical comments, which we incorporated as appropriate.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, the Secretary of HHS, and other interested parties. In addition, the report is available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or dickenj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix II.

Sincerely yours,

John E. Dicken
Director, Health Care

Appendix I: 2017 Medicare and Medicaid Spending on Reference Standard Drugs Subject to REMS

In order to estimate Medicare and Medicaid spending on reference standard drugs subject to risk evaluation and mitigation strategies (REMS), we compared data from the Food and Drug Administration (FDA) on drugs subject to REMS as of March 18, 2019, to publicly available 2017 data on the Medicare Part D Drug Spending Dashboard and the Medicaid Drug Spending Dashboard, maintained by the Centers for Medicare & Medicaid Services (CMS).[1] These data covered drug spending and utilization for both of these programs for calendar year 2017, the most current data available.[2] However, not all spending and utilization data for reference standard drugs subject to REMS were available. Since we analyzed data as of March 18, 2019, we were able to identify 139 reference standard drugs subject to REMS with corresponding cost data.[3] To assess the reliability of these data, we

[1]REMS are safety programs FDA can require for certain drugs with serious safety concerns to ensure that the benefits of a drug outweigh the risks. Reference standard drugs are the products generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is available, it is also designated as the reference standard drug. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug.

The Medicare Part D Drug Spending Dashboard is an interactive, web-based tool that presents spending information for Medicare Part D drugs—drugs that patients generally administer themselves and that are paid through the Medicare Part D program (which represents approximately 70 percent of Medicare beneficiaries). The Medicaid Drug Spending Dashboard is another interactive, web-based tool that presents spending information for drugs paid through the Medicaid program. Medicaid drug data represent national-level drug utilization data for covered outpatient drugs paid for by state Medicaid agencies.

[2]Not all spending data for Medicare and Medicaid were included in the data. For example, drugs with fewer than 50 Medicare and Medicaid claims in 2017 were excluded from their respective data. Also, some reference standard drugs subject to REMS were approved after 2017 and, thus, would not appear in CMS's spending data.

[3]Of the 143 reference standard drugs subject to REMS in our analysis, we identified four with duplicate cost data. We excluded these four duplicates, resulting in 139 reference standard drugs subject to REMS used in our analysis of Medicare and Medicaid drug spending. Of these 139 reference standard drugs subject to REMS, we were able to obtain corresponding cost data for 83 of them, or for approximately 60 percent. Medicare spending data represent total spending for the prescription claim, including amounts paid by the Medicare Part D plan and beneficiary (co-pays), and do not reflect any manufacturer price concessions, such as manufacturers' rebates. Data are payments also based on gross drug cost, which includes ingredient cost, dispensing fees, sales tax, and applicable vaccine administration fees. Medicaid drug spending represents the total amount reimbursed by both Medicaid and non-Medicaid entities (such as third-party payers) to pharmacies for drugs. It includes both federal and state reimbursement and includes any applicable dispensing fees. Additionally, the total is not reduced or affected by Medicaid rebates paid to the states.

interviewed knowledgeable agency officials. We determined that the data were sufficiently reliable for the purposes of our report.

Medicare and Medicaid paid at least $11.8 billion in 2017 for reference standard drugs subject to REMS, according to cost data available from the CMS's drug pricing dashboard.[4] Specifically, Medicare Part D paid at least $8.5 billion for reference standard drugs subject to REMS. This amount—which includes Medicare Part D plan sponsors and beneficiaries Part D payments such as copays, but not price concessions, such as manufacturers' rebates—accounted for at least 8 percent of all Medicare drug spending in 2017.[5] Similarly, Medicaid paid at least $3.3 billion for reference standard drugs subject to REMS, or at least 15 percent of all Medicaid drug spending in 2017.[6]

Of the 139 reference standard drugs in our analysis, the greatest share of these programs' spending, across medical conditions, was on reference standard drugs subject to REMS for cancer, based on our analysis of available data. Specifically, Medicare and Medicaid spent at least $4.6 billion on 8 reference standard drugs that treat cancer. See table 3 below for Medicare and Medicaid spending for reference standard drugs subject to REMS by medical condition treated.

[4]For CMS's Dashboard with spending data, see https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/index.html.

[5]Part D is Medicare's voluntary prescription drug benefit. Private companies, known as Part D plan sponsors, contract with the CMS to provide drug coverage to Medicare beneficiaries. Price concessions are payments that are negotiated between the private insurance companies and drug manufacturers to reduce the private insurance companies' drug costs. Rebates from drug manufacturers are the most common type of price concessions.

Overall, Medicare accounted for approximately $101 billion in spending for retail prescription drugs in 2017. CMS, National Health Expenditure Accounts 2017, Table 4.

[6]Medicaid spent approximately $21.3 billion for drugs in 2017. CMS, National Health Expenditure Accounts 2017, Table 19.

Table 3: Medicare and Medicaid Spending for Selected Reference Standard Drugs Subject to REMS, 2017

Medical conditions treated (number of drugs with available spending data)	Medicare spending (billions of dollars)[a]	Medicaid spending (billions of dollars)[b]	Total Medicare and Medicaid spending (billions of dollars)
Cancer (8)	4.3	0.3	4.6
Pain (42)	1.7	1.3	3.0
Cardiology, respiratory (6)	1.6	0.3	1.9
Viral (1)	0.4	0.6	1.0
Central Nervous System (4)	0.3	0.4	0.7
Total	**8.2**	**3.0**	**11.2**

Source: GAO analysis of data from the Food and Drug Administration (FDA) on drugs with risk evaluation and mitigation strategies (REMS) and data from the Medicare Part D Drug Spending Dashboard and the Medicaid Drug Spending Dashboard, maintained by the Centers for Medicare & Medicaid Services. | GAO-20-94

Note: REMS are drug safety programs that FDA can require for certain drugs with serious safety concerns to ensure the benefits of the drug outweigh the risks. A generic drug company does not have to provide independent evidence of safety and effectiveness for a proposed generic drug. Instead, the company relies on FDA's findings that a previously approved drug is safe and effective and must demonstrate that the generic drug is the same as and bioequivalent to the approved drug, or the reference listed drug When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug. Analysis is based on available cost data for 139 reference standard drugs. Not all Medicare and Medicaid spending data for reference standard drugs subject to REMS were available. Numbers may not sum to exact amounts due to rounding.

[a]Medicare spending is based on gross drug cost, which includes ingredient cost, dispensing fees, sales tax, and applicable vaccine administration fees. It also represents total spending for the prescription claim, including amounts paid by the Medicare Part D plan and beneficiary payments, and do not reflect any price concessions, such as manufacturers' rebates. Price concessions are payments that are negotiated between the private insurance companies and drug manufacturers to reduce the private insurance companies' drug costs. Rebates from drug manufacturers are the most common type of price concessions. In 2017, more than 58 million people were enrolled in Medicare.

[b]Medicaid drug spending represents the total amount reimbursed by both Medicaid and non-Medicaid entities (such as third party payers) to pharmacies for drugs. It includes both federal and state spending and includes any applicable dispensing fees. Additionally, the total is not reduced or affected by Medicaid rebates paid to the states. In 2017, about 74 million people were enrolled in Medicaid.

Further, our analysis of available data showed that Medicare and Medicaid spent the most on Revlimid, a drug used to treat cancer, totaling $3.6 billion with Medicare accounting for $3.3 billion of this total. More than 37,000 Medicare beneficiaries used this drug, at an average cost per dosage unit of $626.94.[7] (See table 4.)

[7]Dosage units for Medicare refer to the form in which the drug is marketed, such as the number of tablets or grams.

Table 4: Medicare Spending for Selected Reference Standard Drugs Subject to REMS, 2017

Reference Standard drug (medical condition treated)	Utilization by Medicare beneficiaries[a]	Average cost ($) per dosage unit paid by Medicare[b]	Medicare spending (billions of dollars)[c]
Revlimid (cancer)	37,459	626.94	3.3
Oxycontin (pain)	193,016	8.50	0.8
Pomalyst (cancer)	7,704	711.31	0.6
Letairis (cardiology, respiratory)	7,741	307.73	0.6
Truvada (viral)	36,552	52.85	0.4
Total			**5.8**

Source: GAO analysis of data from the Food and Drug Administration (FDA) on drugs with risk evaluation and mitigation strategies (REMS) and data from the Medicare Part D Drug Spending Dashboard maintained by the Centers for Medicare & Medicaid Services. | GAO-20-94

Note: REMS are drug safety programs that FDA can require for certain drugs with serious safety concerns to ensure the benefits of the drug outweigh the risks. A generic drug company does not have to provide independent evidence of safety and effectiveness for a proposed generic drug. Instead, the company relies on FDA's findings that a previously approved drug is safe and effective and must demonstrate that the generic drug is the same as and bioequivalent to the approved drug, or the reference listed drug. When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug. Analysis is based on available cost data for 139 reference standard drugs. Not all Medicare spending data for reference standard drugs subject to REMS were available. Numbers may not sum to exact amounts due to rounding.

[a]Utilization is based on the number of beneficiaries that used these drugs.

[b]Dosage units for Medicare refer to the form in which the drug is marketed, such as the number of tablets or grams.

[c]Medicare spending is based on gross drug cost, which includes ingredient cost, dispensing fees, sales tax, and applicable vaccine administration fees. It also represents total spending for the prescription claim, including amounts paid by the Medicare Part D plan and beneficiary payments, and do not reflect any price concessions, such as manufacturers' rebates. In 2017, more than 58 million people were enrolled in Medicare.

In contrast, Medicaid spent the most on Suboxone, a drug used to treat opioid dependence, totaling $0.7 billion, based on available data. More than 3 million Medicaid claims were filed for this drug in 2017, at an average cost per dosage unit of $7.89.[8] Vivitrol was the third most utilized drug under Medicaid. (See table 5.)

[8]Utilization for Medicaid beneficiaries was based on the number of claims filed for this drug in 2017 because data on the number of beneficiaries using this were not available. Dosage unit for Medicaid refers to the drug unit in the lowest dispensable amount. Additionally, the average cost per dosage unit is weighted to account for variation in claim volume for specific drugs, strength, dosage form, routes of administration, and manufacturer levels.

Table 5: Medicaid Spending for Selected Reference Standard Drugs Subject to REMS, 2017

Reference Standard drug (medical conditions treated)	Claims filed by Medicaid beneficiaries[a]	Average cost ($) per dosage unit paid by Medicaid[b]	Medicaid spending (billions of dollars)[c]
Suboxone (opioid dependence)	3,245,841	7.89	0.7
Truvada (viral)	374,754	51.41	0.6
Revlimid (cancer)	20,043	610.98	0.3
Sabril (central nervous system)	15,874	118.50	0.2
Vivitrol (pain)	162,291	1,308.59	0.2
Total			**2.0**

Source: GAO analysis of data from the Food and Drug Administration (FDA) on drugs with risk evaluation and mitigation strategies (REMS) and data from the Medicaid Drug Spending Dashboard, maintained by the Centers for Medicare & Medicaid Services. | GAO-20-94

Note: REMS are drug safety programs that FDA can require for certain drugs with serious safety concerns to ensure the benefits of the drug outweigh the risks. A generic drug company does not have to provide independent evidence of safety and effectiveness for a proposed generic drug. Instead, the company relies on FDA's findings that a previously approved drug is safe and effective and must demonstrate that the generic drug is the same as and bioequivalent to the approved drug, or the reference listed drug.. When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug. Analysis is based on available cost data for 139 reference standard drugs. Not all Medicaid spending data for reference standard drugs subject to REMS were available. Numbers may not sum to exact amounts due to rounding.

[a]Utilization is based on claims filed because the number of beneficiaries using these drugs were not available.

[b]Dosage unit for Medicaid refers to the drug unit in the lowest dispensable amount. Additionally, the average cost per dosage unit is weighted to account for variation in claim volume for specific drugs, strength, dosage form, routes of administration, and manufacturer levels.

[c]Medicaid drug spending represents the total amount reimbursed by both Medicaid and non-Medicaid entities (such as third party payers) to pharmacies for drugs. It includes both federal and state spending and includes any applicable dispensing fees. Additionally, the total is not reduced or affected by Medicaid rebates paid to the states. In 2017, about 74 million people were enrolled in Medicaid.

Based on our analysis of available data, the selected examples of reference standard drugs subject to REMS had higher average cost per dosage unit compared to the generic. For example, Medicare spent an average cost per unit of $12.20 for Clozaril, a drug used to treat mental health conditions, compared to $0.99 for clozapine, a generic version of Clozaril. Table 6 below shows selected examples comparing Medicare spending for reference standard drugs to Medicare spending for a generic version, based on our analysis of available data.

Table 6: Selected Example Comparison of Cost and Utilization of One Reference Standard Drug Subject to REMS and One Generic Version by Medical Conditions Treated Paid by Medicare, 2017

Medical condition treated (drug type)	Utilization by Medicare beneficiaries[a]	Average cost ($) per dosage unit paid by Medicare[b]	Medicare spending (millions of dollars)[c]
Immunology			
Cellcept (reference standard drug)	1,064	13.35	12.5
Mycophenolate mofetil (generic drug)	27,019	0.69	12.9
Mental health			
Clozaril (reference standard drug)	924	12.20	12.2
Clozapine (generic drug)	8,045	0.99	4.7
Fazaclo (reference standard drug)	720	17.96	7.2
Clozapine orally dissolving tablet (generic drug)	3,150	9.89	19.5

Source: GAO analysis of data from the Food and Drug Administration (FDA) on drugs with risk evaluation and mitigation strategies (REMS) and data from the Medicare Part D Drug Spending Dashboard maintained by the Centers for Medicare & Medicaid Services. | GAO-20-94

Note: REMS are drug safety programs that FDA can require for certain drugs with serious safety concerns to ensure the benefits of the drug outweigh the risks. A generic drug company does not have to provide independent evidence of safety and effectiveness for a proposed generic drug. Instead, the company relies on FDA's findings that a previously approved drug is safe and effective and must demonstrate that the generic drug is the same as and bioequivalent to the approved drug, or the reference listed drug. When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug. Analysis is based on available cost data for 139 reference standard drugs. Not all Medicare spending data for reference standard drugs subject to REMS were available. Numbers may not sum to exact amounts due to rounding.

[a]Utilization is based on the number of beneficiaries that used these drugs.

[b]Dosage units for Medicare refer to the form in which the drug is marketed, such as the number of tablets or grams.

[c]Medicare spending is based on gross drug cost, which includes ingredient cost, dispensing fees, sales tax, and applicable vaccine administration fees. It also represents total spending for the prescription claim, including amounts paid by the Medicare Part D plan and beneficiary payments, and do not reflect any price concessions, such as manufacturer rebates. In 2017, more than 58 million people were enrolled in Medicare.

Our analysis of available Medicaid data showed similar results to our analysis of Medicare data. For example, Medicaid spent an average cost of $11.71 for Clozaril, a drug used to treat mental health conditions, compared to $0.97 for clozapine, a generic version Clozaril. Table 7 below shows selected examples comparing Medicaid spending for reference standard drugs to Medicaid spending for a generic version, based on our analysis of available data.

Table 7: Selected Example Comparison of Cost and Utilization of One Reference Standard Drug Subject to REMS with One Generic Version by Medical Conditions Treated Paid by Medicaid, 2017

Medical condition treated (drug type)	Claims filed by Medicaid beneficiaries[a]	Average cost ($) per dosage unit paid by Medicaid[b]	Medicaid spending (millions of dollars)[c]
Immunology			
Cellcept (reference standard drug)	11,775	7.64	11.7
Mycophenolate mofetil (generic drug)	104,025	0.52	7.7
Mental health			
Clozaril (reference standard drug)	2,774	11.71	3.2
Clozapine (generic drug)	29,356	0.97	1.8
Fazaclo (reference standard drug)	9,070	16.90	8.3
Clozapine orally dissolving tablet (generic drug)	29,740	11.41	14.5

Source: GAO analysis of data from the Food and Drug Administration (FDA) on drugs with risk evaluation and mitigation strategies (REMS) and data from the Medicaid Drug Spending Dashboard maintained by the Centers for Medicare & Medicaid Services. | GAO-20-94

Note: REMS are drug safety programs that FDA can require for certain drugs with serious safety concerns to ensure the benefits of the drug outweigh the risks. A generic drug company does not have to provide independent evidence of safety and effectiveness for a proposed generic drug. Instead, the company relies on FDA's findings that a previously approved drug is safe and effective and must demonstrate that the generic drug is the same as and bioequivalent to the approved drug, or the reference listed drug. When the reference listed drug is available, it is also designated as the reference standard drug, which is the product generic drug companies must use to conduct bioequivalence testing. When the reference listed drug is not available, FDA will select an approved generic of the reference listed drug to serve as the reference standard drug. Analysis is based on available cost data for 139 reference standard drugs. Not all Medicaid spending data for reference standard drugs subject to REMS were available. Numbers may not sum to exact amounts due to rounding.

[a]Utilization is based on claims filed because the number of beneficiaries using these drugs were not available.

[b]Dosage unit for Medicaid refers to the drug unit in the lowest dispensable amount. Additionally, the average cost per dosage unit is weighted to account for variation in claim volume for specific drugs, strength, dosage form, routes of administration, and manufacturer levels.

[c]Medicaid drug spending represents the total amount reimbursed by both Medicaid and non-Medicaid entities (such as third party payers) to pharmacies for drugs. It includes both federal and state spending and includes any applicable dispensing fees. Additionally, the total is not reduced or affected by Medicaid rebates paid to the states. In 2017, about 74 million people were enrolled in Medicaid.

Appendix II: GAO Contact and Staff Acknowledgments

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Staff Acknowledgments

In addition to the contact named above, Geri Redican-Bigott and Tom Conahan, Assistant Directors; Carolyn Garvey, Analyst-in-Charge; Zhi Boon, Gay Hee Lee, and McKenna Storey made key contributions to this report. Also contributing were Sam Amrhein, Kaitlin Farquharson, Cathy Hamann, and Diona Martyn.

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