



March 2018

FOOD AND DRUG ADMINISTRATION

Information on Mifeprax Labeling Changes and Ongoing Monitoring Efforts

Accessible Version

GAO Highlights

Highlights of [GAO-18-292](#), a report to congressional requesters

Why GAO Did This Study

FDA initially approved Mifeprex in 2000 and restricted the drug's distribution to assure its safe use. In 2011, the agency approved a REMS for the drug. In March 2016, FDA approved an application for changes to the indication and dosing regimen for Mifeprex, which were reflected in revised labeling. Other changes included omitting the requirement that the prescriber be a physician. At that time, FDA also made modifications to the REMS. Some have questioned the safety implications of these changes for women using the drug.

GAO was asked to review FDA's relabeling of Mifeprex. GAO describes (1) the information FDA used to make its decisions regarding the relabeling of Mifeprex; and (2) what FDA's monitoring of Mifeprex has revealed, and stakeholders' views of FDA's monitoring and the safety of the drug.

GAO reviewed documents related to Mifeprex's relabeling, including FDA policies and regulations. GAO analyzed adverse event reports related to Mifeprex and reviewed FDA inspection reports of Mifeprex's sponsor. GAO also examined studies and data related to the safety and use of Mifeprex, and obtained information from FDA officials; Mifeprex's sponsor; and 13 stakeholder organizations, including medical associations and advocacy groups selected on the basis of their medical or scientific expertise. View [GAO-18-292](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

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What GAO Found

The Food and Drug Administration (FDA) followed its standard review process when it approved the application and revised labeling reflecting certain changes, including the indication and dosing regimen, for the drug Mifeprex, which is used for the medical termination of early pregnancy. It based its approval on reviews of peer-reviewed published studies, articles, and other information submitted by Mifeprex's sponsor. These studies focused on topics related to the proposed labeling changes, including revision of the dosing regimen, increased gestational age, method of follow-up care, and type of health care provider authorized to prescribe Mifeprex. FDA also received three letters from advocacy groups requesting that FDA revise the Mifeprex labeling in a manner that would reflect clinical practice. In addition, FDA reviewed the Risk Evaluation and Mitigation Strategy (REMS)—a set of restrictions beyond the label that FDA may impose—associated with Mifeprex, and determined it continued to be necessary. FDA also reviewed adverse events—which the agency refers to as any untoward medical event associated with the use of a drug in humans, whether or not the event is considered to be drug related—associated with Mifeprex. It determined that the rates of certain adverse events remained stable and acceptably low. In addition, FDA reviewed information regarding potential risks of specific conditions associated with the use of Mifeprex and revised the labeling accordingly. FDA determined that the information it reviewed supported the changes to the Mifeprex labeling.

FDA has conducted a variety of monitoring activities and these have not identified significant concerns with the safety and use of Mifeprex, in accordance with its approved REMS.

- FDA has conducted three inspections of Mifeprex's sponsor since 2008 regarding adverse event reporting associated with Mifeprex—in 2010, 2014, and 2016—and identified minor deficiencies, such as the use of an outdated reporting form.
- FDA conducted a REMS compliance inspection in 2014 and did not identify any deficiencies.
- FDA identified approximately 4,200 instances of adverse events associated with Mifeprex from September 28, 2000, through June 30, 2017, among the approximately 3.2 million women who have used the drug. FDA identified 20 deaths in this period—a rate much lower than for women who proceeded to live birth. FDA learned of 2 additional deaths associated with Mifeprex since June 30, 2017.

GAO found that the views of stakeholder organizations were mixed regarding FDA's monitoring of Mifeprex. Positive comments included that the agency has a comprehensive monitoring program and a robust adverse event reporting system. Criticisms included that adverse events may be underreported and that FDA may only be aware of a fraction of them. Similarly, stakeholder organizations shared mixed views on the drug's safety. Positive comments

included that the mortality rate associated with Mifeprex is extremely low. Safety concerns included that the revised labeling no longer requires patients to have a second visit with a health care provider, and that certain safety issues may be exacerbated by the increased gestational age limit approved by FDA.

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March 28, 2018

Congressional Requesters

The prescription drug Mifeprex, in combination with the prescription drug misoprostol, is used for the medical termination of early pregnancy. The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), initially granted marketing approval of Mifeprex in September 2000. As a condition of the drug's approval, FDA imposed restrictions on the distribution of Mifeprex under its general authority to help assure the safety and effectiveness of new drugs.¹ More than 3 million women in the United States are estimated to have used this drug.

We have previously reported on FDA's approval of Mifeprex and its oversight of the drug's safety, including the restrictions the agency placed on the drug's distribution.² Since that time, in 2011, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex, with the goal of informing patients about the benefits and risks of Mifeprex, and to minimize the risk of serious complications associated with the drug.³ In May 2015, Mifeprex's sponsor proposed several changes to the administration of the drug.⁴ It submitted a supplemental new drug application to FDA to obtain approval to revise the drug's labeling.⁵

¹See 21 C.F.R. § 314.520 (2000).

²GAO, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, [GAO-08-751](#), (Washington, D.C.: Aug. 7, 2008).

³A REMS is a set of restrictions specifically authorized by statute that FDA may impose to ensure that a drug's benefits outweigh its risks. See 21 U.S.C. § 355-1.

⁴A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable provisions of laws, such as the Federal Food, Drug, and Cosmetic Act and related regulations. Danco Laboratories, L.L.C., the sponsor of Mifeprex, is responsible for the marketing and manufacturing of Mifeprex, and submitted the supplemental application to FDA.

⁵Supplemental new drug applications are submitted to make certain changes to already approved new drug applications, including adding or modifying an indication or claim, or revising the dose or dosing regimen. FDA review and approval of most types of supplemental new drug applications is required before the drug may be marketed with these changes. FDA characterized the supplemental application submitted for Mifeprex as an efficacy supplement that, among other things, revised its dosing regimen. See 21 C.F.R. § 314.3 (2017). Throughout this report, references to the Mifeprex application pertain to this supplemental new drug application, submitted as an efficacy supplement.

Among other things, the sponsor proposed changing the dosing regimen, increasing the gestational age limit up to which Mifeprex can be taken, and eliminating the requirement that the dose of misoprostol be administered in a medical facility. FDA approved the labeling change in March 2016 and determined that the REMS continued to be necessary, with some modifications.

You and others have questioned whether the revised Mifeprex labeling has safety implications for the women who use the drug. For example, some stakeholder organizations, such as medical associations and research organizations, have raised concerns regarding FDA's postmarketing monitoring of Mifeprex and the drug's safety.⁶ You asked us to report on FDA's relabeling of Mifeprex and its monitoring activities. This report describes

1. the information FDA used to make its decisions regarding the relabeling of Mifeprex; and
2. what FDA's monitoring of Mifeprex has revealed, and stakeholders' views of FDA's monitoring and the safety of the drug.

To describe the information FDA used to make its decisions regarding the relabeling of Mifeprex, we obtained information regarding the agency's review and subsequent approval of the revised Mifeprex labeling. Specifically, we reviewed documents in FDA's approval package for the Mifeprex supplemental new drug application. The approval package included FDA's assessments of the published literature submitted by Mifeprex's sponsor to support the safety and efficacy of the proposed changes.⁷ Additionally, we reviewed other documents in the approval package, including communications between FDA and Mifeprex's sponsor during the application process, and the revised Mifeprex labeling and REMS. In addition, we studied FDA's assessments of adverse events associated with Mifeprex.⁸ Finally, we examined federal regulations and FDA's policies and guidance documents, and interviewed FDA officials.

⁶The term postmarketing refers to activities occurring after a drug has been approved for marketing.

⁷FDA has posted documents pertaining to its review and approval on the agency's website (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm).

⁸FDA uses the term adverse event to refer to any untoward medical event associated with the use of a drug in humans, whether or not the event is considered to be drug related.

To describe how FDA monitors the safety and use of Mifeprex, we analyzed FDA's postmarketing adverse event summary reports associated with the use of Mifeprex from September 28, 2000, (when the drug was approved) through June 30, 2017, and obtained information from FDA officials regarding the agency's monitoring activities.⁹ We also reviewed quarterly adverse event summary reports submitted to FDA by Mifeprex's sponsor for fiscal year 2017. To further describe FDA's monitoring, we reviewed documentation from inspections the agency conducted to determine the sponsor's compliance with relevant regulations and the Federal Food, Drug, and Cosmetic Act. Specifically, we reviewed FDA's reports from inspections of Mifeprex's sponsor for compliance with adverse event reporting requirements and the Mifeprex REMS that were performed since our 2008 report was issued.¹⁰ We obtained information from FDA on the number and results of inspections that FDA has conducted since 2008 for compliance with current good manufacturing practices.¹¹ We also reviewed studies and data related to the safety and use of Mifeprex from FDA, stakeholders, and other entities. We discussed FDA's data collection processes and any limitations with agency officials and determined that the data we used were sufficiently reliable for the purposes of this report. We also obtained information from Mifeprex's sponsor on its perspectives of FDA's monitoring. Finally, to describe stakeholders' views of FDA's monitoring and the safety of the drug, we obtained information from 13 organizations, including medical associations and advocacy groups with a variety of perspectives for their

⁹FDA officials said that the adverse events associated with Mifeprex in its summary reports do not necessarily reflect a conclusion by the company or FDA that the drug caused or contributed to an adverse event. See 21 C.F.R. § 314.80(l) (2017).

¹⁰See [GAO-08-751](#).

¹¹Current good manufacturing practices provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-21 (2017).

views on FDA's monitoring of Mifeprex, including any safety-related concerns they may have about the drug.¹²

We conducted this performance audit from April 2017 to March 2018 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

The treatment regimen of taking Mifeprex, in combination with misoprostol, works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.¹³ Mifepristone, the active ingredient in Mifeprex, was first approved in France and China in 1988, and is now approved in approximately 60 other countries, including the United States.

¹²We obtained information from the following 13 organizations: the American Association of Pro-Life Obstetricians and Gynecologists; American College of Pediatricians; American Congress of Obstetricians and Gynecologists; Association of Reproductive Health Professionals; Bixby Center for Global Reproductive Health, University of California San Francisco; Charlotte Lozier Institute; Family Research Council; Guttmacher Institute; Gynuity Health Projects and the lead author of the Mifeprex REMS Study Group; Institute for Safe Medication Practices; National Right to Life Committee; Office of Population Research, Princeton University; and Planned Parenthood Federation of America. We selected these organizations on the basis of their medical or scientific expertise, their publication of relevant articles and web-based materials, or their familiarity with the safety and use of Mifeprex.

¹³Mifeprex is the trade name for one of the two mifepristone products approved and marketed in the United States (the trade name for the other product is Korlym, which has a different, unrelated indication). Mifepristone is the underlying drug substance and is also sometimes called RU-486, a reference to the name the drug had during laboratory testing. Medical abortion terminates a pregnancy using medications, rather than through a surgical procedure.

FDA's Review of New Drug Applications and Supplemental Applications

FDA must approve an application for a new drug before it can be marketed in the United States. FDA reviews scientific and clinical data contained in these applications as part of its process in considering them for approval to be marketed. FDA initially approved Mifeprex for use in the United States on September 28, 2000.¹⁴ FDA approved the drug subject to restrictions that it considered necessary to ensure safe usage.

In addition to reviewing applications to market new drugs, FDA reviews supplemental new drug applications that drug sponsors submit to propose changes to an approved drug, such as adding or modifying an indication, revising the dose or dosing regimen, providing for a new route of administration, or changing the marketing status from prescription to over-the-counter use. As with original new drug applications, the agency assembles an internal team of reviewers—including medical officers, chemists, statisticians, pharmacologists, and other experts—to evaluate the information submitted in a supplemental application. During the review process, FDA may communicate with sponsors about issues that arise that may affect the approvability of the supplemental application. In response, sponsors can submit additional information to FDA in the form of amendments to the pending supplemental application. The review team compiles the results of its analyses and recommends to FDA management whether the supplemental application should be approved. Once the review is completed, the agency issues an action letter to the sponsor. FDA may approve the supplemental application (approval letter) or, if it determines it will not approve the supplemental application in its present form, it describes the specific deficiencies it identified in the supplemental application (complete response letter).

The review process for a drug application, including a supplemental application, may span several cycles before the agency approves the

¹⁴In general, the mifepristone treatment regimens approved in other countries were similar to the regimen approved in the United States, although in some cases the specific drug used in combination with mifepristone was different than misoprostol.

application.¹⁵ For those applications that receive a complete response letter during a review cycle, the next FDA review cycle begins once the sponsor resubmits its application, providing responses to the deficiencies FDA identified in its previous review. These resubmissions often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The agency's review team examines the additional information provided by the sponsor, conducts any additional analyses that are required, studies the results of any additional inspections that have been conducted, and again recommends either an approval or complete response action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the review team and makes its decision on the action to take on the application.

Mifeprex's Supplemental Application

Prior to submitting its supplemental application, Mifeprex's sponsor met with FDA officials on January 29, 2015, to discuss the proposed labeling and Mifeprex REMS changes. At this meeting, both parties agreed that the sponsor should submit a supplemental new drug application covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.¹⁶ On May 29, 2015, Mifeprex's sponsor submitted a supplemental application to FDA to revise the dosing regimen, amend the Mifeprex labeling, and modify the Mifeprex REMS. FDA's review for this supplemental application was classified as a standard review—as opposed to a priority review—with the performance goal of completing the application review

¹⁵The first review cycle begins when FDA receives an application from a sponsor and ends when FDA issues an action letter. If FDA does not approve the application during the first review cycle, a new review cycle begins if the sponsor resubmits the application to provide responses to the deficiencies identified by FDA in the previous review cycle. See 21 CFR § 314.110(b)(1) (2017).

¹⁶This pertains to new drug applications that rely, at least in part, on investigations that “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted” See 21 U.S.C. § 355(b)(2). For example, such an application may rely on the finding of safety or effectiveness for an approved product or on published literature in addition to studies conducted by the sponsor.

and issuing an action letter to Mifeprex's sponsor within 10 months.¹⁷ FDA approved the supplemental application on March 29, 2016, after one review cycle, meeting the agency's performance goal for the timely review of supplemental applications.¹⁸ Table 1 shows key components of the original Mifeprex regimen and the revised regimen.

¹⁷FDA generally grants priority review to applications for drugs that treat serious conditions and that, if approved, would provide significant improvements in safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies. FDA has a performance goal for completing priority reviews of supplemental applications in 6 months. FDA assigns a standard review designation to applications for drugs that do not meet the priority review designation criteria. FDA's goal is to generally complete review of these applications in 10 months.

¹⁸Food and Drug Administration, Mifeprex label, March 2016, accessed January 25, 2018, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

Table 1: Key Components of the Original Mifeprex Regimen and Prescriber Requirements, Approved in 2000, and the Revised Mifeprex Regimen and Prescriber Requirements, Approved in 2016

Regimen component	Original regimen	Revised regimen
Dosage	600 mg Mifeprex (mifepristone); 400 mcg misoprostol	200 mg Mifeprex (mifepristone); 800 mcg misoprostol
Dosing regimen	Day 1: 600 mg Mifeprex in a single oral dose. Day 3: 400 mcg misoprostol in a single oral dose if termination of pregnancy is not complete.	Day 1: 200 mg Mifeprex in a single oral dose. Day 2 or 3: 800 mcg misoprostol by buccal route (i.e., in the cheek pouch), 24 to 48 hours after taking Mifeprex.
Maximum gestational age (since first day of last menstrual period)	49 days	70 days
Prescriber requirements	To become certified, a licensed physician must sign and return the Prescriber Agreement Form to Mifeprex’s sponsor. ^a	To become certified, a healthcare provider who prescribes must sign and return the Prescriber Agreement Form to Mifeprex’s sponsor. ^a
Office visits and follow-up visits with prescriber, and location of dosing administration	Required three office visits by the patient: (1) 600 mg of Mifeprex administered to the patient by the physician or under the supervision of the physician in a clinic, medical office, or hospital. (2) Patient returns on day three for examination with physician; if termination of pregnancy is not complete, physician administers 400 mcg of misoprostol for patient to take orally. (3) Patient returns to physician for follow-up visit approximately 14 days after administration of Mifeprex to confirm complete termination of the pregnancy occurred.	Requires one office visit by the patient: (1) 200 mg of Mifeprex administered to the patient by the healthcare provider who prescribes, or under the supervision of a healthcare provider who prescribes, in a clinic, medical office, or hospital. (2) Patient takes 800 mcg of misoprostol by buccal route 24 to 48 hours after Mifeprex administration; the healthcare provider who prescribes discusses with the patient an appropriate location for her to be when she takes the misoprostol. (3) Patient should follow up with healthcare provider who prescribes approximately 7 to 14 days after Mifeprex administration to confirm complete termination of pregnancy has occurred and to evaluate the degree of bleeding.
Repeat misoprostol dose, if necessary	N/A	If the pregnancy has ended, but complete expulsion did not occur after the initial dose of misoprostol, the patient may be prescribed an additional 800 mcg of misoprostol to take buccally; women who choose to take a repeat dose of misoprostol should have a follow-up visit with their healthcare provider who prescribes in approximately 7 days to assess for complete expulsion.

Source: GAO analysis of information from the Food and Drug Administration. | GAO-18-292

^aBy signing the Prescriber Agreement Form, the prescriber certifies that he or she agrees with all specified requirements, including that the sponsor’s Medication Guide will be supplied to all patients.

Mifeprax REMS

FDA initially approved a REMS for Mifeprax in June 2011.¹⁹ When FDA approved the revised Mifeprax labeling in March 2016, the agency determined the REMS continued to be necessary, with some modifications.²⁰ Modifications from the original REMS to the revised REMS included

- changing the requirement that Mifeprax be provided “by or under the supervision of a physician” meeting specified qualifications to “by or under the supervision of a healthcare provider who prescribes” and meets such qualifications;
- changing the requirement for prescribers to agree to report to Mifeprax’s sponsor any serious adverse event associated with Mifeprax, including hospitalizations and blood transfusions, to requiring prescribers to agree to report deaths associated with Mifeprax to the sponsor;²¹
- requiring Mifeprax’s sponsor to report to FDA any death associated with Mifeprax, whether or not the death was considered drug-related, no later than 15 calendar days from the initial receipt of the information);²² and
- removing the Medication Guide (which contained specific patient information, such as how to take Mifeprax and potential side effects) as an element of the REMS, although the Medication Guide remains part of the approved Mifeprax labeling, and the revised REMS requires the healthcare provider to provide a copy of the Medication Guide to the patient.²³

¹⁹As part of a REMS, FDA can require “elements to assure safe use,” 21 U.S.C. § 355-1(f)(1). This may include restrictions similar to those required to assure safe use under which Mifeprax was originally approved. 21 C.F.R. § 314.520 (2000).

²⁰Food and Drug Administration, Mifeprax Risk Evaluation and Mitigation Strategy, March 2016, accessed January 25, 2018, https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprax_2016-03-29_REMS_full.pdf.

²¹This requirement does not affect the sponsor’s other reporting requirements under federal regulations.

²²This requirement does not affect the sponsor’s other reporting requirements under federal regulations.

²³See 21 C.F.R. 208.24 (2017).

As part of the REMS, Mifeprex's sponsor is required to submit REMS assessments to FDA. The first REMS assessment was due one year from the date of initial approval of the REMS. Subsequent assessments are due every three years thereafter.²⁴ The REMS assessments include data on the cumulative number of health care providers enrolled in the Mifeprex REMS program; the number of providers ordering Mifeprex during the assessment reporting period; and the number of women exposed to Mifeprex, both cumulative and during the reporting period. In addition, they include copies of reports for certain adverse events, including hospitalizations due to complications, blood transfusions, serious infections, and deaths, as well as the cumulative numbers of these adverse events since the approval of Mifeprex and the number during the reporting period.

FDA's Postmarketing Oversight Activities

Federal regulations require sponsors of approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with their use.²⁵ Sponsors must provide in periodic reports—quarterly for the first three years after approval and annually thereafter—a narrative summary and analysis of adverse event information to FDA. For adverse events that are considered both serious and unexpected, sponsors are required to submit a Postmarketing 15-day Alert Report to FDA within 15 calendar days of initial receipt of the information.²⁶

In some instances, FDA may request sponsors to study matters that it has determined worthy of further examination. Such requests are known as postmarketing study commitments and include studies or clinical trials that FDA has requested—and sponsors have agreed to conduct—to

²⁴Mifeprex's sponsor submitted its first REMS assessment to FDA in June 2012, and the second one in June 2015.

²⁵See 21 C.F. R. § 314.80 (2017).

²⁶Serious adverse events are those that result in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of an existing hospitalization, a significant or persistent disability or incapacity, or a congenital anomaly or birth defect. Unexpected adverse events are those that are not included in the current labeling for a drug. Adverse events associated with a drug do not necessarily imply the drug caused the event.

address such issues.²⁷ FDA requires sponsors to report on the status of these studies in an annual report that also includes other information such as updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.²⁸ FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA conducts postmarketing adverse drug experience inspections of sponsors to assess compliance with adverse event reporting requirements. FDA also conducts inspections of sponsors' compliance with the REMS, as applicable.²⁹ In addition, FDA inspects manufacturers for compliance with current good manufacturing practices. FDA classifies the results of each type of inspection in one of three ways:

- A classification of "official action indicated" means that objectionable conditions were found that may warrant regulatory action by the agency.
- A classification of "voluntary action indicated" means that objectionable conditions that do not meet the threshold for regulatory action were identified, and any corrective actions are left to the establishment to take voluntarily.
- A classification of "no action indicated" means that no objectionable conditions or practices were found during the inspection, or that the significance of the documented objectionable conditions found does not justify further FDA action.

To monitor and analyze adverse events associated with an approved drug, FDA compiles data from sponsors' reports on adverse events, as well as data from voluntary reports submitted to the MedWatch program, all of which are entered into FDA's Adverse Event Reporting System

²⁷See Pub. L. No. 105-115, § 130, 111 Stat. 2296, 2331-2 (codified at 21 U.S.C. § 356b). Sponsors may also be required to conduct additional postmarketing studies or clinical trials (i.e., in connection with accelerated approval of drugs for serious conditions or approval based on animal efficacy data, or where determined necessary to identify or assess a serious risk related to use of a drug). See 21 U.S.C. §§ 355(o) (serious risk), 356(c)(2)(A) (accelerated approval); 21 C.F.R. § 314.610(b)(1) (2017) (animal efficacy data).

²⁸See 21 C.F. R. § 314.81(b)(2) (2017).

²⁹In 2008, we reported that FDA conducted three postmarketing adverse drug experience inspections of Mifeprex's sponsor in 2002, 2004, and 2006. The REMS for Mifeprex was not in place at that time. See [GAO-08-751](#).

(FAERS).³⁰ FDA also established the Sentinel System, which may be used to monitor drugs using electronic health care data. This system complements FDA's existing monitoring capabilities, such as FAERS, by providing administrative and claims data that can be queried to monitor the use of FDA-regulated medical products and potential outcomes of treatment. The Sentinel System currently includes reimbursement data related to diagnoses, procedures, and drugs dispensed to over 223 million patients derived from 17 different data partnerships, including national health insurers and managed care organizations. While reimbursed health care encounters, procedures, and medications are included in the Sentinel System, those that are not reimbursable—such as visits to free health care clinics, drug samples given in physicians' offices, use of low-cost generic medications that do not incur an insurance copayment, or over-the-counter medications—generally are not captured.

FDA Reviewed Published Studies that Supported the Efficacy of the Proposed Mifeprex Labeling Changes, and Evaluated Safety Information and Adverse Event Data

In considering the supplemental application to revise the Mifeprex labeling, FDA reviewed 62 studies and articles that were submitted by the drug's sponsor related to different aspects of the efficacy and safety of the proposed changes. Over the course of FDA's application review, the agency also requested and received more detailed information from the authors of select publications through communication with Mifeprex's sponsor. Additionally, FDA evaluated adverse event data associated with Mifeprex.

³⁰MedWatch is a voluntary reporting system through which health professionals and consumers can report adverse reactions, product problems, and errors in use related to drugs and other products approved by FDA.

FDA Reviewed Numerous Studies in Considering the Efficacy of the Proposed Changes to the Mifeprex Labeling

To determine the efficacy of the proposed changes to the Mifeprex labeling, FDA reviewed numerous published studies submitted by Mifeprex's sponsor, which included both U.S. and international studies.³¹ Some of these studies assessed the efficacy of one component of the proposed Mifeprex labeling changes, such as the dosing regimen. Other studies assessed more than one component, such as home administration of misoprostol and the gestational age limit for Mifeprex. FDA also requested and received more detailed information from the authors of select publications through communication with Mifeprex's sponsor. In their review of the application, FDA reviewers identified what they considered major proposed changes. Some of the published studies submitted by Mifeprex's sponsor that FDA reviewed to support each of these proposed changes included the following:

- **Changes to the proposed dose and dosing regimen.** FDA reviewed 30 studies that evaluated changes to the dose and dosing regimen. For example, 22 of these studies, collectively, evaluated over 35,000 women who took the proposed dosing regimen—200 milligrams of Mifeprex orally and 800 micrograms of misoprostol buccally (i.e., in the cheek pouch) 24 to 48 hours after Mifeprex administration. The efficacy rates, defined as complete termination of the pregnancy without need for surgical intervention for any reason, ranged from 91 percent to 98 percent. One of these publications summarized the results of 20 studies, all but one of which used the proposed Mifeprex regimen in gestations through 70 days.³² The overall efficacy rates in these 20 studies ranged from 97 percent to 98 percent for those studies that provided this information.

³¹FDA accepts the use of peer-reviewed literature as primary or supportive data for an application under the framework of a 505(b)(2) application. See U.S.C. 21 § 355(b)(2). As part of its submission to FDA, Mifeprex's sponsor noted that it did not provide financial support or sponsor any of the studies submitted in its supplemental application. FDA's webpage pertaining to its review and approval of the Mifeprex supplemental application includes review documents (e.g., Cross Discipline Team Leader Review and Medical Review(s) documents) that contain lists and tables of references citing the publications FDA reviewed in the supplemental application (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm).

³²M.J. Chen and M.D. Creinin, "Mifepristone with Buccal Misoprostol for Medical Abortion: A Systematic Review," *Obstetrics & Gynecology*, vol. 126, no.1 (2015): 12-21.

- **Extending the gestational age to 70 days.** FDA reviewed 19 studies that evaluated increasing the gestational age limit for taking Mifeprex. In addition to the publication discussed above that summarized the results of 20 studies, 4 of the studies that FDA reviewed evaluated the proposed dosing regimen through 70 days gestation.³³ Three of these studies evaluated the efficacy rates for gestational ages of 64 to 70 days, which ranged from 91 percent to 96 percent. The fourth study evaluated the efficacy rates through 70 days gestation when the drug was administered by physician providers (98 percent) and by nurse providers (98 percent). An additional publication submitted by the sponsor was a systematic review of studies that covered various dosing regimens, including the proposed regimen from 64 to 70 days gestation, which had a 93 percent efficacy rate.³⁴ Two other studies evaluated the efficacy rates from 64 to 70 days gestation, but used different dosing regimens than the proposed regimen, with efficacy rates of 92 percent for one study and 95 percent for the other study.³⁵ The remaining 11 studies evaluated efficacy rates for gestation greater than the then-approved 49 days gestation, but less than 64 days, with efficacy rates ranging from 87 percent to 100 percent.
- **Home administration of misoprostol.** FDA reviewed 15 studies that evaluated home administration of misoprostol, although FDA reported

³³The four studies were: (1) B. Winikoff, I.G. Dzuba, E. Chong, et al., "Extending Outpatient Medical Abortion Services through 70 Days of Gestational Age," *Obstetrics & Gynecology*, vol. 120 (2012): 1070-1076; (2) A.A. Boersma, B. Meyboom-de Jong, and G. Kleiverda, "Mifepristone Followed by Home Administration of Buccal Misoprostol for Medical Abortion up to 70 days of Amenorrhoea in a General Practice in Curacao," *The European Journal of Contraception & Reproductive Health Care*, vol. 16 (2011): 61-66; (3) P. Sanhueza Smith, M. Pena, I.G. Dzuba, et al., "Safety, Efficacy and Acceptability of Outpatient Mifepristone-Misoprostol Medical Abortion through 70 days Since Last Menstrual Period in Public Sector Facilities in Mexico City," *Reproductive Health Matters*, vol. 22 (2015): 75-82; and (4) C.D. Olavarrieta, B. Ganatra, A. Sorhaindo, T.S. Karver, A. Seuc, A. Villalobos, S.G. Garcia, M. Pérez, M. Bousiequez, and P. Sanhueza, "Nurse Versus Physician-Provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial," *Bulletin of the World Health Organization*, vol. 93 (2015): 249-258.

³⁴D. Abbas, E. Chong, and E.G. Raymond, "Outpatient Medical Abortion is Safe and Effective through 70 Days Gestation," *Contraception*, vol. 92 (2015):197-199.

³⁵The two studies were: (1) H. Bracken, R. Dabash, G. Tsertsivadze, et al., "A Two-Pill Sublingual Misoprostol Outpatient Regimen following Mifepristone for Medical Abortion through 70 Days' LMP: A Prospective Comparative Open-Label Trial," *Contraception*, vol. 89(3) (2014): 181-186; and (2) E.V. Gouk, et al., "Medical Termination of Pregnancy at 63-83 Days Gestation," *BJOG: An International Journal of Obstetrics and Gynaecology*, vol. 106 (1999): 535-539. FDA noted that these two studies were relevant because the dosage levels and routes of administration were expected to have similar or lower effectiveness than the proposed dosing regimen.

that none of these studies evaluated treatment outcomes with the use of misoprostol at home compared to a clinic setting. However, one study was a large literature review of 87 studies that included over 45,000 women evaluated using a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration, and dosing intervals in gestations through 63 days.³⁶ Half of the studies in this review did not require women to take misoprostol in a clinic. The results showed that the rates of treatment failure and ongoing pregnancy were very similar regardless of whether misoprostol was taken in a clinic or at another location. A further analysis of factors leading to increased failure found no evidence that home use of misoprostol increased rates of treatment failure or serious complications.

- **Use of a repeat misoprostol dose.** FDA reviewed 10 studies to support the use of a repeat dose of misoprostol. This repeat dose would be taken in instances when complete expulsion did not occur after the initial misoprostol dose and Mifeprex dose. For example, one study evaluated 68 women who did not have complete expulsion after taking Mifeprex and were given a second vaginal dose of misoprostol, with an efficacy rate of 62 percent.³⁷ In another study that evaluated the proposed regimen through 70 days gestation, 5 of 330 women took a second dose of misoprostol, because of the absence of bleeding after the first dose of misoprostol. The study found that one of the five women who took the second dose did not achieve the desired result.³⁸ In one other study that evaluated women using the proposed regimen through 63 days gestation, 16 of 863 women received a second dose of misoprostol, with an efficacy rate of 100

³⁶E.G. Raymond and D.A. Grimes, "The Comparative Safety of Legal Induced Abortion and Childbirth in the United States," *Obstetrics & Gynecology*, vol. 119 (2012): 215-219.

³⁷M.F. Reeves, A. Kudva, and M. Creinin, "Medical Abortion Outcomes after a Second Dose of Misoprostol for Persistent Gestational Sac," *Contraception*, vol. 78 (2008): 332-335.

³⁸Boersma, Meyboom-de Jong, and Kleiverda, "Mifepristone Followed by Home Administration of Buccal Misoprostol," 61-66.

percent.³⁹ The other 7 studies had efficacy rates for an additional dose of misoprostol ranging from 67 percent to 100 percent.⁴⁰

- **Follow-up care requirements.** FDA reviewed 11 studies that evaluated different methods for follow-up care after Mifeprex administration. One of these studies, which FDA considered a key publication on this topic, was a review of studies that assessed the impact of the timing of follow-up care.⁴¹ This study found no differences in the failure rates between women who received follow-up care within one week of taking mifepristone compared to those who received follow-up care a week or more after taking mifepristone. The other 10 studies included a variety of study designs and dosing regimens through 63 days gestation, and FDA determined that the various methods of follow up, including home pregnancy testing and phone contact with the patient to inquire about symptoms, were acceptable alternatives to an in-clinic follow up.
- **Change in provider qualifications.** FDA reviewed four studies that addressed the efficacy of medical abortion performed by nonphysician health care providers; three of which used the proposed dosing regimen and one evaluated vaginal administration of misoprostol.⁴² In these studies, almost 1,500 women had gestations through 70 days or more, and over 700 of these women had nonphysician care. In

³⁹K.S. Louie, T. Tsereteli, E. Chong, F. Ailyeva, G. Rzayeva, and B. Winikoff, "Acceptability and Feasibility of Mifepristone Medical Abortion in the Early First Trimester in Azerbaijan," *The European Journal of Contraception & Reproductive Health Care*, vol. 19, no. 6 (2014): 457-464.

⁴⁰Mifeprex's sponsor noted to FDA that approximately 1 percent to 5 percent of women will need a second dose of misoprostol following the initial Mifeprex dosing regimen.

⁴¹E.G. Raymond, et al., "First-Trimester Medical Abortion with Mifepristone 200 mg and Misoprostol: A Systematic Review," *Contraception*, vol. 87 (2013): 26-37.

⁴²The three studies that used the proposed regimen were (1) H. Kopp Kallner, R. Gomperts, E. Salomonsson, M. Johansson, L. Marions, and K. Gemzell-Danielsson, "The Efficacy, Safety and Acceptability of Medical Termination of Pregnancy Provided by Standard Care by Doctors or by Nurse-Midwives: A Randomized Controlled Equivalence Trial," *BJOG: An International Journal of Obstetrics and Gynaecology*, vol. 122 (2015): 510-517; (2) Olavarrieta, Ganatra, Sorhaindo, Karver, Seuc, Villalobos, Garcia, Pérez, Bousiequez, and Sanhueza, "Nurse Versus Physician-Provision of Early Medical Abortion," 249-258; and (3) M. Puri, A. Tamang, P. Shrestha, D. Joshi, "The Role of Auxiliary Nurse-Midwives and Community Health Volunteers in Expanding Access to Medical Abortion in Rural Nepal," *Reproductive Health Matters*, vol. 44 Supplement (2015): 94-103. The study that addressed vaginal misoprostol was: I.K. Warriner, D. Wang, N.T.M. Huong, K. Thapa, A. Tamang, I. Shah, et al., "Can Midlevel Health-Care Providers Administer Early Medical Abortion as Safely and Effectively as Doctors? A Randomized Controlled Equivalence Trial in Nepal," *Lancet*, vol. 377 (2011): 1155-1161.

addition, almost 2,300 women had gestations up to 63 days, and over 1,000 of these women had nonphysician care. The efficacy rates were greater than or equal to 96 percent across all of the studies, regardless of gestational age or provider type.

FDA also received three letters from representatives of advocacy organizations and professional associations—some of which were signed by more than one entity—requesting that FDA revise the Mifeprex labeling in a manner that would reflect then-current clinical practice, including the new dosing regimen and extending the gestational age limit through 70 days.⁴³ Among others, the signers of these letters included the American Congress of Obstetricians and Gynecologists, American Public Health Association, Gynuity Health Projects, Ibis Reproductive Health, and National Abortion Federation. FDA officials told us that the peer-reviewed studies the agency received from external entities (i.e., entities other than Mifeprex’s sponsor) were also submitted by Mifeprex’s sponsor in the supplemental application, which FDA reviewed.⁴⁴ In addition, FDA officials told us that they received letters from organizations that were based on other than scientific perspectives, and FDA officials noted that they only considered scientific information in their review of the Mifeprex supplemental application.

FDA Evaluated Safety Information and Adverse Event Data as Part of Its Assessment of the Proposed Changes to the Mifeprex Labeling

FDA also reviewed published studies submitted by the drug’s sponsor to assess the safety profile of the proposed dosing regimen, including both U.S. and international studies. Of the seven U.S. studies submitted with the Mifeprex supplemental application that examined safety issues, one

⁴³According to FDA, once the agency approves a drug, health care providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient, a practice known as off-label use. FDA also indicated that the proposed changes approved in the Mifeprex supplemental application were consistent with current medical practice.

⁴⁴According to FDA officials, the agency received one study from an external entity that was superseded by a more current publication on the same topic by one of the same authors. In this instance, FDA officials reviewed the more current publication provided by Mifeprex’s sponsor.

specifically addressed deaths associated with Mifeprex.⁴⁵ This study noted that there were no deaths among 578 patients who received the proposed Mifeprex dosing regimen through 63 days gestation. According to FDA, because only one of these studies addressed deaths associated with Mifeprex, this may reflect the fact that it is a rare outcome and, therefore, the absence of reported deaths might not be noted by the authors of a study. In addition, FDA reviewed an observational study from Australia that was also submitted as part of the application. It identified one death from sepsis—a life-threatening complication of an infection—among 13,345 pregnancy terminations using the proposed dosing regimen through 63 days gestation.⁴⁶

In addition to reviewing published studies submitted by Mifeprex's sponsor, FDA reviewed adverse event reports from the drug's approval on September 28, 2000, through November 17, 2015. During this time, there were 17 reported deaths in the United States associated with Mifeprex, and 8 of those were associated with sepsis. Seven of the 8 sepsis cases were associated with vaginal use of misoprostol, which was, but no longer is, a common practice, according to FDA. The agency found that the adverse event data that it reviewed demonstrated that the rates of hospitalizations, severe infections, blood loss requiring transfusion, and complications related to ectopic pregnancy remained stable and acceptably low.

FDA also reviewed common adverse events, such as nausea, vomiting, diarrhea, and fever/chills, reported in U.S. and international studies submitted by Mifeprex's sponsor, and found the reporting of the frequencies of these events was higher in the U.S. studies. However, FDA determined that these differences likely reflected lower reporting of adverse events in international studies. These common adverse events are included in the Mifeprex labeling. The labeling also cites bleeding and cramping, which are expected effects of the drug regimen, according to FDA. Overall, FDA found the rate of deaths and nonfatal serious adverse events associated with Mifeprex to be acceptably low, and data for the proposed regimen did not suggest a safety profile that deviated from that

⁴⁵D. Grossman, K. Grindlay, T. Buchacker, K. Lane, and K. Blanchard, "Effectiveness and Acceptability of Medical Abortion Provided through Telemedicine," *Obstetrics & Gynecology*, vol. 118 (2011): 296-303.

⁴⁶P. Goldstone, J. Michelson, and E. Williamson, "Early Medical Abortion Using Low-Dose Mifepristone Followed by Buccal Misoprostol: A Large Australian Observational Study," *Medical Journal of Australia*, vol. 197 (2012): 282-286.

of the originally approved Mifeprex regimen, which was approved as part of an application with restrictions to assure safe use. In addition, no association between adverse outcomes and increasing gestational age was identified.

In January 2016, FDA completed a review of adverse event data associated with Mifeprex in its FAERS database, as well as the published medical literature, on a potential safety concern regarding anaphylaxis and angioedema associated with mifepristone.⁴⁷ FDA's review of FAERS data found one case of anaphylaxis and six cases of angioedema with mifepristone administration, with six of the seven cases seen in women using mifepristone for pregnancy termination, as opposed to using mifepristone for Cushing's syndrome.⁴⁸ The sole case of anaphylaxis could not be directly attributed to mifepristone because an oral antibiotic (doxycycline) was concomitantly administered, according to FDA. FDA did not find any additional cases of anaphylaxis or angioedema with mifepristone administration in its review of the literature. FDA noted that anaphylaxis was included in the current labeling for misoprostol. Because the approved Mifeprex regimen includes misoprostol, FDA determined that the Mifeprex labeling should also be updated to include anaphylaxis, despite the lack of anaphylaxis cases with mifepristone alone. The addition of angioedema was supported by the FAERS data documented in FDA's review. As a result, anaphylaxis and angioedema were added to the areas of the Mifeprex labeling that address allergic reactions.

The potential risk of uterine rupture was also considered in FDA's review of the Mifeprex supplemental application. FDA reviewers conducted a literature search on this topic, and identified five reports of uterine rupture in studies published from 2000 through 2014; three of which occurred with the combined mifepristone/misoprostol dosing regimen. FDA also completed a review of FAERS from January 1, 1965, through October 15, 2015, for reports of uterine rupture.⁴⁹ Of the 80 reports found in FAERS, 77 cited use of misoprostol alone, and 3 cited use of both mifepristone

⁴⁷Anaphylaxis is a severe, potentially life-threatening allergic reaction. Angioedema is a form of severe swelling beneath the skin's surface.

⁴⁸Cushing's syndrome is a hormonal disorder affecting both men and women caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. Mifepristone is also approved for this indication, under the brand name Korlym.

⁴⁹According to FDA, January 1, 1965, is the date that the FAERS predecessor system was initiated.

and misoprostol. Two reports of uterine rupture in the first trimester were identified in the FAERS review, both using misoprostol alone. One report entailed an unspecified dose and route of misoprostol at 5 weeks gestation. The other report involved vaginal administration of 800 micrograms of misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar. Information regarding this safety concern was added to the Mifeprex labeling when the supplemental application was approved on March 29, 2016. The agency concluded, however, that no restriction of use was needed, because this was an extremely rare adverse event.

FDA concluded that the evidence it reviewed and evaluated, including the revisions to the REMS, demonstrated acceptable safety for the proposed changes to the Mifeprex regimen, and that the dosing regimen had a similar safety profile as the original regimen approved in 2000. The agency further concluded that adverse events of interest—such as deaths, serious infection, transfusions, ectopic pregnancies, and uterine rupture—remained rare, and were not necessarily attributable to Mifeprex use.⁵⁰

FDA's Monitoring Activities Have Not Identified Significant Safety Concerns with Mifeprex; Stakeholders' Views on FDA's Monitoring and the Drug's Safety Were Mixed

FDA's monitoring of Mifeprex—primarily through inspections, and review and analysis of adverse event data—has not identified any significant concerns with the safety and use of Mifeprex. The views of the stakeholder organizations that we contacted regarding FDA's monitoring of the safety of Mifeprex and the safety of the drug itself were mixed.

⁵⁰Similarly, a recently issued study by the National Academies of Sciences, Engineering, and Medicine reported that complications—such as hemorrhage, hospitalization, persistent pain, infection, or prolonged heavy bleeding—are rare after a medical abortion. This study cited some of the same studies FDA relied on and noted that complications occur in no more than a fraction of a percent of patients. National Academies of Sciences, Engineering, and Medicine, *The Safety and Quality of Abortion Care in the United States* (Washington, D.C.: prepublication copy).

FDA's Monitoring Has Not Identified Any Significant Concerns Regarding the Safety and Use of Mifeprex as Marketed with the Approved REMS

Since our prior report was issued in 2008, FDA conducted three postmarketing adverse drug experience inspections of Mifeprex's sponsor—in 2010, 2014, and 2016.⁵¹ It identified minor deficiencies, but no significant safety concerns. These inspections each contained between two and four inspection observations—that is, the investigator observed conditions that, in his or her judgment, constituted violations of applicable federal requirements. In each of these inspections, FDA's final classification was "voluntary action indicated," meaning that objectionable conditions or practices were found, but they did not meet the threshold of regulatory significance. According to agency officials, FDA's practice for inspections resulting in this classification is to review the corrective actions taken by the establishment related to the objectionable conditions or practices during the course of the next regularly scheduled inspection. FDA officials told us that they have not yet scheduled the next postmarketing adverse drug experience inspection.

According to FDA, violations associated with postmarketing adverse drug experience inspections classified as voluntary action indicated are typically technical in nature. Examples of some of the observations from inspections of Mifeprex's sponsor include the following:

- In 2010, the sponsor was found to have used an older version of the form used for mandatory reporting of adverse events (FDA Form 3500A), rather than the more recent version.
- In 2014, two serious adverse events were not reported to FDA within the required 15-day period, and instead were included in the sponsor's subsequent quarterly adverse event report to FDA.
- In 2016, the sponsor's quarterly adverse event reports did not include the required analysis of the Postmarketing 15-day Alert Reports that occurred over the period.

In addition to postmarketing adverse drug experience inspections, Mifeprex's sponsor was subject to a REMS compliance inspection, which the agency conducted in 2014. According to FDA officials, the agency did

⁵¹See [GAO-08-751](#).

not identify any compliance issues and determined that the final classification was no action indicated.

FDA also conducted three inspections since 2008 of the facility where Mifeprex is manufactured to ensure compliance with current good manufacturing practices. FDA did not find any deficiencies during two of these inspections; however, in the other inspection, FDA's findings resulted in a final classification of voluntary action indicated. According to the inspection report, FDA officials found an improperly performed test on a raw material used in another product produced at the same facility, not related to Mifeprex. A subsequent inspection determined that corrective action was taken by the manufacturer.

In addition to inspection data, FDA conducted ongoing monitoring of adverse event data. These data are collected through required reporting, including periodic reports on adverse events provided by the sponsor and reports by the prescriber to the sponsor, which, depending on the event, may be required under the REMS. In addition, voluntary reports may be made by the public. FDA compiled this information into periodic postmarketing adverse event summary reports, the interval of which ranged from 2 to 18 months. These reports show that between September 28, 2000, and June 30, 2017, there were approximately 4,200 reports of adverse events associated with Mifeprex, including approximately 1,000 hospitalizations and 20 deaths.⁵² These deaths represented a reporting rate of 0.0006 percent for the approximately 3.2 million women who have used Mifeprex since 2000. For context, a study of mortality among women who did not have an abortion and proceeded to a live birth estimated a mortality rate of 0.009 percent. Nonfatal adverse events, including blood loss requiring transfusion and infections, were more common among women who took Mifeprex, but still relatively low compared to the number of users. (See table 2.)

⁵²Mifeprex's sponsor reported two additional deaths to FDA that had not yet been included in FDA's periodic adverse event report—one reported in September 2017 and one reported in December 2017. FDA gathers and reports data on adverse events associated with Mifeprex, which are not necessarily caused by Mifeprex. For example, an unrelated health condition observed near the time that a woman took Mifeprex may be included in FDA's adverse event summary data.

Table 2: Adverse Events Associated with Mifeprex Reported to FDA from September 28, 2000, through June 30, 2017

Adverse event category	September 28, 2000 to October 31, 2012 ^a	November 1, 2012 to June 30, 2017 ^a
Number of cases	Number of cases	Number of cases
Any adverse event ^b	2,740	1,439
Specific types of adverse events ^c		
Deaths ^d	14	6
Hospitalization	768	273
Blood loss with transfusion	416	182
Infections	308	103
Ectopic pregnancies	66	31
Severe infections	57	12

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-292

Notes: (1) Approximately 3.2 million women have taken Mifeprex since its initial approval in 2000. (2) An adverse event associated with Mifeprex does not necessarily indicate that Mifeprex caused the event.

^aFDA implemented the FDA Adverse Event Reporting System (FAERS) in 2012, and migrated all the data from the previous reporting system to FAERS. Adverse event summary reports beginning on November 1, 2012, are based on FAERS data. Differences may exist when comparing case counts in FAERS with FDA’s previous reporting system. Therefore, FDA does not recommend calculating a cumulative number for the data in table 2, with the exception of the case counts for deaths and ectopic pregnancies. These data were harmonized by FDA and may be added.

^bAny adverse event includes all the categorized adverse events listed below it (i.e., deaths, hospitalization, blood loss with transfusion, infections and severe infections, and ectopic pregnancies), as well as other noncategorized events.

^cOf the six types of categorized adverse events, only deaths are solely recorded as such—that is, they are not reflected in the tally for other categorized adverse events. The remaining categories are overlapping, meaning that a single case could be counted within multiple categories. Also, the hospitalization category includes both categorized and noncategorized adverse events. According to FDA, the most common adverse events among those that are not categorized (accounting for approximately 94 percent) are vaginal bleeding not requiring transfusion, retained products of conception, ongoing pregnancy, cramping, dizziness, and nausea. Among noncategorized adverse events resulting in hospitalization, the most common is dilation and curettage (accounting for approximately 81 percent).

^dIn addition to the 20 deaths included in FDA’s periodic adverse event reports, the sponsor reported two additional deaths to FDA—one reported in September 2017 and one reported in December 2017—which the agency said will be included in its next periodic adverse event report.

Although postmarketing study commitments or requirements are another method for obtaining additional information about drug safety and use, in the case of Mifeprex the planned studies were deemed by FDA to be infeasible. As we previously reported, FDA originally approved Mifeprex subject to the sponsor’s commitment to conduct two postmarketing studies.⁵³ For the first study, the sponsor agreed to assess whether

⁵³See [GAO-08-751](#).

clinical outcomes were similar for patients under the care of providers who possessed the surgical intervention skills to perform a surgical abortion compared with patients of providers who did not have such skills and referred patients for surgical abortions. FDA said the sponsor reported that the number of physicians who prescribed Mifeprax and did not possess the surgical intervention skills to perform a surgical abortion was so small that such a study was not feasible. FDA agreed and released them from that commitment in September 2008. For the second study, the sponsor was required to examine, through a surveillance and reporting system, the outcomes of pregnancies where the drug regimen failed to result in their termination. According to FDA officials, Mifeprax's sponsor reported to FDA that over nearly 2 years of monitoring (January 2006 through November 2007) there were one or two instances per year of the drug not resulting in termination. The sponsor told FDA that this was, in part, because patients had to consent to being monitored, resulting in a very small number of participants. Given these low numbers, FDA agreed that this study was also not feasible.

We also found that FDA's Sentinel System, which was developed to enhance the agency's ability to monitor postmarketing safety, is not a viable option for monitoring the use of Mifeprax. Although it contains millions of records, the Sentinel System is based on administrative and claims data, and only reimbursed health care encounters, procedures, and medications are captured in the system. Because of the REMS restrictions placed on the drug's distribution, Mifeprax is not dispensed in pharmacies. Instead, it is only available under certain conditions and from certain clinics, medical offices, and hospitals. Therefore, according to FDA officials, the Sentinel System does not include a sufficient number of Mifeprax dispensings to generate valid results. Nonetheless, we asked FDA to query the Sentinel System for mifepristone (the active pharmaceutical ingredient for Mifeprax) beginning in 2000, when the drug was first approved. The results of this query showed that, until 2012, mifepristone registered a small number of drug dispensings. Specifically, between 2000 and 2011, only 12 individuals were identified as potentially exposed to mifepristone. However, from 2012 through 2016, 243 individuals were identified, including both men and women. FDA officials explained that another drug—Korlym, which treats Cushing's syndrome and contains the same active pharmaceutical ingredient as Mifeprax—

became available in 2012.⁵⁴ Even with additional dispensings beginning in 2012, FDA officials said there were still insufficient data captured to enable a robust safety assessment.

Stakeholder Organizations Had Mixed Views on FDA's Monitoring of Mifeprex and of Mifeprex's Safety

The views of the stakeholder organizations that provided us with information on FDA's monitoring of the safety and use of Mifeprex, and the safety of the drug itself, were mixed. Stakeholders provided positive comments regarding FDA's monitoring of Mifeprex and also made suggestions to improve what they considered to be weaknesses. Positive comments included that

- FDA had a very comprehensive monitoring program that mandated the reporting of serious adverse events associated with Mifeprex up through 2016. In light of the low rates of nonfatal adverse events and the good safety profile of Mifeprex, FDA no longer requires providers to report nonfatal adverse events.
- FDA is properly monitoring the safety and use of Mifeprex through a robust adverse event reporting system, and FDA is doing its due diligence, based on the agency's mission, to identify any safety issues with the drug.
- FDA's requirement that Mifeprex be subject to a REMS has made it more likely that adverse events would be reported. Specifically, additional contacts with health care providers, as is required by the Mifeprex REMS in the form of prescriber certification and patient education, generally lead to higher adverse event reporting rates than drugs without such requirements.

Stakeholders that either commented that FDA's monitoring efforts could be improved or that expressed concern about the agency's ability to know the extent of potential safety issues said, for example, that

- FDA may only be aware of a fraction of adverse events associated with Mifeprex. There are anecdotal examples of adverse events, such

⁵⁴The analysis that was conducted in the Sentinel System only recognizes the active pharmaceutical ingredient and does not distinguish between the drugs dispensed, according to FDA officials. The data show both men and women receiving mifepristone since 2012. Korlym's dose of mifepristone is significantly higher than that of Mifeprex and, unlike Mifeprex, the drug is taken by patients on an ongoing basis.

as severe bleeding, that may not be reported as such or that may be interpreted by emergency health care providers as a natural miscarriage. Underreporting may get worse under the revised Mifeprex label, which eliminates the follow-up visit and does not require prescribers to report nonfatal adverse events.

- FDA may not have reliable data on the number of women who have used Mifeprex, which would affect the denominator for tracking adverse events. With an unclear denominator, FDA may not have an accurate measure of adverse event rates associated with Mifeprex.

Regarding the safety of Mifeprex, stakeholders we contacted provided a mix of favorable comments about the drug, as well as certain safety concerns. Positive comments included the following

- The mortality rate associated with Mifeprex is extremely low—about one fourteenth the mortality rate associated with live birth.
- Nonfatal serious adverse events following Mifeprex use, such as hospital admission, blood transfusion, or serious infection, are also rare, occurring at rates ranging from 0.01 percent to 0.7 percent, and are almost always treatable without permanent effects. Side effects, such as bleeding, cramping, fever, and chills, are typically minor and transient.
- In the years since mifepristone’s approval, multiple clinical trials, dozens of studies, and extensive experience across the globe have confirmed FDA’s finding that mifepristone is a safe and reliable method of abortion. Thus, any significant concern about the safety of Mifeprex would be unwarranted.

Stakeholders also expressed some concerns about Mifeprex’s safety. For example, they reported that

- Mifeprex may be linked to hemorrhaging and serious infections. A study was cited that showed adverse events were more likely to be associated with a medical abortion rather than a surgical abortion.⁵⁵ Two other studies were cited that examined the effect mifepristone may have on the body’s ability to control hemorrhaging and prevent

⁵⁵M. Niinimäki, et al., “Immediate Complications after Medical Compared with Surgical Termination of Pregnancy,” *Obstetrics & Gynecology*, vol. 114, no. 4 (October 2009): 795-804. This study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that, overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients.

serious infections.⁵⁶ For example, one of the studies found that serious bacterial infection and sepsis may occur without the usual signs of infection with the use of mifepristone for medical abortion.

- Safety issues may be exacerbated by the Mifeprex labeling changes. For example, a study was cited that found that the rates of pregnancy termination with Mifeprex dropped from 92 percent up to the 7th week of gestation to 77 percent at the 9th week.⁵⁷
- Women in the later weeks of pregnancy who live far from a health care provider may be at increased risk of serious hemorrhaging under the revised labeling, which does not require a second visit with a health care provider.

In addition, another comment we heard was that the agency was being too restrictive by continuing to require a REMS for the drug. Specifically, we were told that Mifeprex should not continue to be restricted to being dispensed at a clinic, medical office, or hospital—as it is under the Mifeprex REMS—because ample research shows Mifeprex to be safe and adverse events to be rare. Stakeholders also noted that women in rural areas may have less access to the drug, and Mifeprex’s sponsor commented that the distribution restrictions likely result in the drug being less accessible than it otherwise would be.⁵⁸

In response to the concerns regarding Mifeprex that we heard from stakeholder organizations, FDA officials said that the agency approved the supplemental application for Mifeprex under the same approval standards that it applies to all new drug applications and supplemental applications, and found that the data and information submitted in the supplemental application demonstrated that Mifeprex is safe and effective

⁵⁶R.P. Miech, “Pathopharmacology of Excessive Hemorrhage in Mifepristone Abortions,” *Annals of Pharmacotherapy*, vol. 41, no. 12 (December 2007): 2002-2007. See also, R.P. Miech, “Pathophysiology of Mifepristone-induced Septic Shock due to *Clostridium sordellii*,” *Annals of Pharmacotherapy*, vol. 39, no. 9 (September 2005): 1483-1488.

⁵⁷I. M. Spitz, C. W. Bardin, L. Benton, and A. Robbins, “Early Pregnancy Termination with Mifepristone and Misoprostol in the United States,” *New England Journal of Medicine*, vol. 338, no. 18 (Apr. 30, 1998): 1241-1247.

⁵⁸In October 2017, a doctor and several professional health associations filed a lawsuit in the U.S. District Court for the District of Hawaii to challenge the distribution restrictions imposed by FDA under the Mifeprex REMS. *Chelius, et al. v. Wright*, No. 17-cv- 00493 (D. Hawaii, filed Oct. 3, 2017). Plaintiffs argued that REMS requirements may be imposed only when necessary to ensure that a drug’s benefits outweigh its risks, and that restrictions requiring Mifeprex to be distributed through clinics or hospitals do not meet the criteria.

for its intended use. FDA officials noted that Mifeprex also has a REMS in place to ensure safety. They also stressed that, as with all FDA-approved drugs, Mifeprex is subject to adverse event reporting requirements and continued postmarketing safety monitoring by the agency.

Agency Comments

We provided a draft of this report for comment to HHS. HHS provided technical comments, which we incorporated as appropriate. We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

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



Marcia Crosse
Director, Health Care

List of Requesters

The Honorable Robert Aderholt
Chairman
Subcommittee on Agriculture, Rural Development,
Food and Drug Administration, and Related Agencies
Committee on Appropriations
House of Representatives

The Honorable Tom Cole
House of Representatives

The Honorable Chuck Fleischmann
House of Representatives

The Honorable Jeff Fortenberry
House of Representatives

The Honorable Tom Graves
House of Representatives

The Honorable Andy Harris
House of Representatives

The Honorable Steven Palazzo
House of Representatives

The Honorable Kevin Yoder
House of Representatives

Appendix I: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact above, Geri Redican-Bigott (Assistant Director), Lisa A. Lusk (Analyst-in-Charge), George Bogart, Drew Long, and Perry Parsons made key contributions to this report. Kaitlin Farquharson also made contributions to this report.

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