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FILED IN THE DISTRICT COURT
OKLAHOMA COUNTY, OKLA.
JAN 26 2012
PATRICIA PRESLEY, COURT CLERK
by _____ DEPUTY

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

(1) OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of itself and its members; and (2) NOVA HEALTH SYSTEMS, D/B/A REPRODUCTIVE SERVICES, on behalf of itself, its staff, and its patients, Plaintiffs, v. (3) TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health; and, (4) LYLE KELSEY, in his official capacity as Executive Director of the Oklahoma State Board of Medical Licensure and Supervision; and, (5) CATHERINE C. TAYLOR, in her official capacity as the President of the Oklahoma State Board of Osteopathic Examiners, Defendants.	Case No. CV-2011-1722 Judge Daniel L. Owens

PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Pursuant to Rule 13(a) of the Rules for District Courts of Oklahoma, Okla. Stat. tit. 12, ch. 2, app., Rule 13(a), Plaintiffs move this Court for summary judgment on the claims in Plaintiffs' Petition. Plaintiffs seek entry of (1) a declaratory judgment that Oklahoma House Bill 1970, 2011 Okla. Sess. Laws ch. 216 (amending Okla. Stat. tit. 63, § 1-729a) (the "Act"), violates the Oklahoma Constitution and is therefore unenforceable; and (2) a permanent injunction, without bond, restraining Defendants, their employees, agents, and successors in office from enforcing the Act. In support of this motion, Plaintiffs submit the accompanying memorandum of law; a copy of the Act (attached hereto as Appendix 1); the

Declaration of Lisa D. Rarick, M.D., with exhibits (attached hereto as Appendix 2); a report, numbered GAO-08-751, from the United States Government Accountability Office (attached hereto as Appendix 3); the Declaration of Daniel A. Grossman, M.D., with exhibits (attached hereto as Appendix 4); the Declaration of Dana Stone, M.D., with exhibits (attached hereto as Appendix 5); the Declaration of Abigail Long, with exhibits (attached hereto as Appendix 6); the Declaration of Marilyn Eldridge (attached hereto as Appendix 7); the Declaration of Martha Skeeters, Ph.D. (attached hereto as Appendix 8); and an excerpt of The Oklahoma State Constitution: A Reference Guide (attached hereto as Appendix 9). The grounds for this motion are as follows:

1. The claims that are the subject of the instant motion do not involve any substantial controversy as to material facts and are appropriate for summary disposition;
2. The Act attempts to delegate to the United States Food and Drug Administration the Legislature's authority and responsibility to establish policy for the State of Oklahoma regarding the practice of medicine, in violation of the non-delegation doctrine derived from Articles IV and V of the Oklahoma Constitution;
3. The Act violates the equal protection rights of patients seeking pregnancy terminations and physicians who provide that medical care, in violation of Art. II, § 7, of the Oklahoma Constitution;
4. The Act is an impermissible special law under Art. V, § 59, of the Oklahoma Constitution;
5. The Act is vague in violation of the due process clause of the Oklahoma Constitution, Okla. Const. art. II, § 7;
6. The Act violates the right to abortion and the right to bodily integrity secured to

women in Oklahoma by the due process clause of the Oklahoma Constitution, Okla. Const. art. II, § 7;

7. The Act forces physicians to make factually untrue statements, in violation of Art. II, § 22, of the Oklahoma Constitution;
8. Plaintiffs and those whose interests they represent will suffer irreparable harm from enforcement of the Act;
9. Plaintiffs are entitled to a declaratory judgment that the Act violates the Oklahoma Constitution and is, therefore, unenforceable; and
10. Plaintiffs are entitled to a permanent injunction, without bond, restraining Defendants, their employees, agents, and successors in office from enforcing the Act.

Respectfully submitted this 26th of January, 2012

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** Admitted to practice by order dated Oct. 7, 2011*

ATTORNEYS FOR PLAINTIFFS

CERTIFICATE OF SERVICE

I hereby certify that on the 26th day of January, 2012, true and correct copies of the foregoing motion and supporting papers were delivered by electronic mail to the following:

Patrick R. Wyrick
Solicitor General
Office of the Attorney General
313 N.E. 21st Street
Oklahoma City, Oklahoma 73105
Email: patrick.wyrick@oag.ok.gov

ANNE E. ZACHRITZ

Appendix 1

ENROLLED HOUSE
BILL NO. 1970

By: Grau, Trebilcock, Cockroft, Reynolds, Faught, Ownbey, Kern, Ritze, Cooksey, Roberts (Dustin) and Peterson of the House

and

Treat, Brecheen and Allen of the Senate

An Act relating to public health and safety; amending Section 1, Chapter 48, O.S.L. 2010 (63 O.S. Supp. 2010, Section 1-729a), which relates to RU-486 for the purpose of inducing abortions; adding definitions; requiring that physicians prescribe certain drugs according to certain protocol; modifying duties of certain physicians; requiring physician to examine woman and document gestational age prior to administering certain drugs; requiring follow-up appointment to be scheduled for certain patient; providing for severability; and providing an effective date.

SUBJECT: Abortion

BE IT ENACTED BY THE PEOPLE OF THE STATE OF OKLAHOMA:

SECTION 2. AMENDATORY Section 1, Chapter 48, O.S.L. 2010 (63 O.S. Supp. 2010, Section 1-729a), is amended to read as follows:

Section 1-729a. A. As used in this section:

1. Abortion-inducing drug means a medicine, drug, or any other substance prescribed or dispensed with the intent of terminating the clinically diagnosable pregnancy of a woman, with knowledge that the termination shall with

reasonable likelihood cause the death of the unborn child. This includes off-label use of drugs known to have abortion-inducing properties, which are prescribed specifically with the intent of causing an abortion, such as misoprostol (Cytotec), and methotrexate. This definition does not apply to drugs that may be known to cause an abortion, but which are prescribed for other medical indications, such as chemotherapeutic agents or diagnostic drugs;

2. Drug label or drug s label means the pamphlet accompanying an abortion-inducing drug which outlines the protocol tested and authorized by the U.S. Food and Drug Administration (FDA) and agreed upon by the drug company applying for FDA authorization of that drug. Also known as final printing labeling instructions , it is the FDA document which delineates how a drug is to be used according to the FDA approval;

3. Federal law means any law, rule, or regulation of the United States or any drug approval letter of the U.S. Food and Drug Administration that governs or regulates the use of RU-486 (mifepristone) or any abortion-inducing drug for the purpose of inducing abortions;

~~2.~~ 4. Personal identifying information means any information designed to identify a person and any information commonly used or capable of being used alone or in conjunction with any other information to identify a person; and

~~3.~~ 5. Physician means a doctor of medicine or osteopathy legally authorized to practice medicine in the state.

B. No person shall knowingly or recklessly give, sell, dispense, administer, prescribe, or otherwise provide RU-486, also known as mifepristone, or any abortion-inducing drug for the purpose of inducing an abortion in a pregnant female, unless the person who gives, sells, dispenses, administers, prescribes, or otherwise provides the RU-486 (mifepristone) or any abortion-inducing drug is a physician who:

1. Has the ability to assess the duration of the pregnancy accurately;

2. Has the ability to diagnose ectopic pregnancies;

3. Has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made and documented in the patient s medical record plans to provide such care through other qualified physicians;

4. Is able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and

5. Has read and understood the prescribing information for the use of RU-486 (mifepristone) or any abortion-inducing drug as provided by the drug manufacturer in accordance with the requirements of the U.S. Food and Drug Administration.

C. No physician who provides RU-486 (mifepristone) or any abortion-inducing drug shall knowingly or recklessly fail to provide or prescribe the RU-486 (mifepristone) or any abortion-inducing drug according to the protocol tested and authorized by the U.S. Food and Drug Administration and as authorized in the drug label for the RU-486 (mifepristone) or any abortion-inducing drug.

D. No physician who provides RU-486 (mifepristone) or any abortion-inducing drug for the purpose of inducing an abortion shall knowingly or recklessly fail to:

1. Provide each patient with a copy of the drug manufacturer s medication guide and drug label for RU-486 (mifepristone) or any abortion-inducing drug being used;

2. Fully explain the procedure to the patient, including, but not limited to, explaining ~~whether the physician is using~~ that the drug is being used in accordance with the protocol tested and authorized by the U.S. Food and Drug Administration ~~regimen or an evidence-based regimen, and, if using an evidence-based regimen, specifying that the regimen differs from the U.S. Food and Drug Administration regimen and providing detailed information on the evidence-based regimen being used~~ and as outlined in the drug label for RU-486 (mifepristone) or any abortion-inducing drug;

3. Provide the female with a copy of the drug manufacturer s patient agreement and obtain the patient s signature on the patient agreement;

4. Sign the patient agreement; and

5. Record the drug manufacturer s package serial number in the patient s medical record.

~~D.~~ E. Because the failure and complications from medical abortion increase with increasing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because RU-486 (mifepristone) or any abortion-inducing drug does not treat ectopic pregnancies but rather is contraindicated in ectopic pregnancies, the physician giving, selling, dispensing, administering, or otherwise providing or prescribing

RU-486 (mifepristone) or any abortion-inducing drug shall first examine the woman and document, in the woman s medical chart, gestational age and intrauterine location of the pregnancy prior to giving, selling, dispensing, administering, or otherwise providing or prescribing RU-486 (mifepristone) or any abortion-inducing drug.

F. When RU-486 (mifepristone) or any abortion-inducing drug is used for the purpose of inducing an abortion, the drug must be administered ~~by or~~ in the same room and in the physical presence of the physician who prescribed, dispensed, or otherwise provided the drug to the patient. The physician inducing the abortion, or a person acting on behalf of the physician inducing the abortion, shall schedule the patient for a follow-up appointment and make all reasonable efforts to ensure that the patient returns twelve (12) to eighteen (18) days after the administration or use of RU-486 (mifepristone) or any abortion-inducing drug for a follow-up visit so that the physician can confirm that the pregnancy has been terminated and assess the patient s medical condition. A brief description of the efforts made to comply with this subsection, including the date, time, and identification by name of the person making such efforts, shall be included in the patient s medical record.

~~E.~~ G. 1. If a physician provides RU-486 (mifepristone) or any abortion-inducing drug for the purpose of inducing an abortion and if the physician knows that the female who uses the RU-486 (mifepristone) or any abortion-inducing drug for the purpose of inducing an abortion experiences within one (1) year after the use of RU-486 (mifepristone) or any abortion-inducing drug an incomplete abortion, severe bleeding, or an adverse reaction to the RU-486 (mifepristone) or any abortion-inducing drug or is hospitalized, receives a transfusion, or experiences any other serious event, the physician shall, as soon as is practicable, but in no case more than sixty (60) days after the physician learns of the adverse reaction or serious event, provide a written report of the incomplete abortion, severe bleeding, adverse reaction, hospitalization, transfusion, or serious event to the drug manufacturer. If the physician is a doctor of medicine, the physician shall simultaneously provide a copy of the report to the State Board of Medical Licensure and Supervision. If the physician is a doctor of osteopathy, the physician shall simultaneously provide a copy of the report to the State Board of Osteopathic Examiners. The relevant Board shall compile and retain all reports it receives pursuant to this subsection. All reports the relevant Board receives under this subsection are public records open to inspection pursuant to the Oklahoma Open Records Act; however, absent an order by a court of competent jurisdiction, neither the drug manufacturer nor the relevant Board shall release the name or any other personal identifying information regarding a person who uses or provides RU-486 (mifepristone) or any abortion-inducing drug for the purpose of inducing an abortion and who is the subject of a report the drug

manufacturer or the relevant Board receives under this subsection.

2. No physician who provides RU-486 (mifepristone) or any abortion-inducing drug to a pregnant female for the purpose of inducing an abortion shall knowingly or recklessly fail to file a report required under paragraph 1 of this subsection. Knowing or reckless failure to comply with this subsection shall subject the physician to sanctioning by the licensing board having administrative authority over such physician.

~~F.~~ H. Any female upon whom an abortion has been performed, the father of the unborn child who was the subject of the abortion if the father was married to the woman who received the abortion at the time the abortion was performed, or a maternal grandparent of the unborn child~~,~~ may maintain an action against the person who performed the abortion in knowing or reckless violation of this section for actual and punitive damages. Any female upon whom an abortion has been attempted in knowing or reckless violation of this section may maintain an action against the person who attempted to perform the abortion for actual and punitive damages.

~~G.~~ I. If a judgment is rendered in favor of the plaintiff in any action described in this section, the court shall also render judgment for a reasonable attorney fee in favor of the plaintiff against the defendant. If a judgment is rendered in favor of the defendant and the court finds that the plaintiff s suit was frivolous and brought in bad faith, the court shall also render judgment for a reasonable attorney fee in favor of the defendant against the plaintiff.

~~H.~~ J. No pregnant female who obtains or possesses RU-486 (mifepristone) or any abortion-inducing drug for the purpose of inducing an abortion to terminate her own pregnancy shall be subject to any action brought under subsection ~~F~~ H of this section.

K. If some or all of the language in this section is ever temporarily or permanently restrained or enjoined by judicial order, then this section shall be enforced as though such restrained or enjoined provisions had not been adopted; provided, however, that whenever such temporary or permanent restraining order or injunction is stayed or dissolved, or otherwise ceases to have effect, such provisions shall have full force and effect.

SECTION 2. This act shall become effective November 1, 2011.

Passed the House of Representatives the 4th day of May, 2011.

Presiding Officer of the House of Representatives

Passed the Senate the 26th day of April, 2011.

Presiding Officer of the Senate

Appendix 2

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of its members, ET AL.,	)	
Plaintiffs,	)	Case No. CV-2011-1722
v.	)	
TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health, ET AL.,	)	Judge Daniel L. Owens
Defendants.	)	

DECLARATION OF LISA D. RARICK, M.D. IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

LISA D. RARICK, M.D. hereby declares, under penalty of perjury, that the following statements are true and correct:

1. I provide the following facts and opinions as an expert in reproductive health and the regulation of drugs by the United States Food and Drug Administration ("FDA"). I am a Board-certified obstetrician-gynecologist licensed to practice medicine in the State of Maryland and the District of Columbia. I worked at the FDA from 1988 to 2003. A copy of my curriculum vitae, which summarizes my professional experience, is annexed hereto as Exhibit A.

2. My work at the FDA began with a part-time position in the Center for Drug Evaluation and Research ("CDER") investigating the effects of drug exposure on fetal development. Later, I became a full-time Medical Officer in the Division of Metabolic and Endocrine Drug Products. In 1996, I was named Director of the newly created Division of Reproductive and Urologic Drug Products. While in that position, I became well-acquainted

with the new drug application ("NDA") for mifepristone. I participated in the review of that NDA and the Advisory Committee meetings concerning mifepristone. In 1999, I was promoted to Deputy Office Director for the Office of Drug Evaluation 2, and in 2000, I was promoted to Associate Director of CDER for Quality Assurance. In 2002, I moved to the Office of the Commissioner, where I served as a Medical Officer in the Office of Women's Health.

3. I left the FDA in 2003 and have been working as a private consultant since then, providing consulting services to pharmaceutical companies, venture capital firms, advocacy groups, and individuals regarding regulatory affairs and reproductive health.

FDA Approval of Medications and Labeling

4. FDA approval of a drug means that the manufacturer may sell or market the drug in the United States. In other words, it allows the manufacturer to make the drug available to U.S. populations. The FDA neither authorizes nor limits physicians' use of FDA-approved drugs, because the FDA does not regulate the practice of medicine. Physicians are expected to use FDA-approved products in the most appropriate way for their patients.

5. The Final Printed Labeling ("FPL") for an FDA-approved drug is an informational document that provides physicians with guidance about how to use a drug in accordance with how the drug sponsor requested and received FDA approval for its use. It does not impose binding obligations on a physician and it cannot authorize or limit any use of a drug. Moreover, an FPL is not an FDA document. It is an FDA-approved document, for which the drug manufacturer has ultimate responsibility.

6. The FDA does not require drug manufacturers to list all possible uses for a drug in the drug's FPL, no matter how much information about possible uses is in the medical literature. A drug manufacturer gets to choose what the FPL says about the uses for which the manufacturer

wants to market the drug. For example, there is information in the medical literature about the ways that misoprostol is helpful in abortions, but the manufacturers have not decided to label or market Cytotec that way, so the FPL for Cytotec does not have information about that use.

7. After a drug has been approved by the FDA, physicians may prescribe it for indications and in dosages other than what is set forth in the drug's FPL. That common practice by physicians is known as "off-label" use.

8. It is extremely important for physicians to have multiple treatment options in providing care, even though different options will have different risks and benefits. Every individual is different, and has different pharmacokinetics; the art of prescribing is in determining the best treatment for the particular patient. No clinical trial can identify the perfect treatment for everyone.

9. In guidance documents, the FDA has repeatedly acknowledged that off-label use is common and is sometimes required by good medical practice.

10. For example, in an April 1982 *"FDA Drug Bulletin,"* this topic was specifically addressed. Here the FDA stated that "...The FD&C Act does not...limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature." The Bulletin goes on to state: "....accepted medical practice often includes drug use that is not reflected in approved drug labeling." A copy of that FDA Drug Bulletin is annexed hereto as Exhibit B.

11. Similarly, in a 2004 Guidance for Industry document entitled *IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*, the FDA stated that: "Off-label therapy with cancer drugs is common in practice. When there is no established therapy for a cancer, or stage of cancer, it is common for oncologists to try different regimens or combinations of established drugs. . . . In their daily practice, many oncologists treat cancer patients with regimens that include off-label use of drugs. They evaluate the published data and past clinical experience to assess the risk of such treatments. Such treatment of individual patients with approved drugs within their clinical practice does not require an IND." ("IND" means investigational new drug application.) A copy of that Guidance for Industry document is annexed hereto as Exhibit C.

12. Indeed, in 2010 the FDA reaffirmed its stance in an Information Sheet entitled *"Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices*, stating that: "Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effect." *See* http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm.

13. Off-label use of drugs is particularly common among obstetricians because many drugs are not labeled for use by pregnant women. As one example, the standard of care for treatment and management of premature labor includes the use of several possible drugs including indomethacin, calcium channel blockers and magnesium sulfate. Not one of these products includes information in the FDA-approved labeling for use in this condition.

14. All medications have risks and benefits. The risks and benefits of a particular drug are not affected by the purpose for which a drug is used; they will all apply regardless of the purpose. Differences in dosage, regimen, or characteristics of the particular patient, on the other hand, can affect the risks and benefits of a medication. The balance of risks and benefits, and the acceptability of risks, depends on the circumstances of the patient for whom a physician is considering prescribing the medication.

FDA Approval of Mifeprex

15. The NDA for mifepristone, which is sold under the brand name Mifeprex and also known as RU-486, was submitted to the FDA in 1996. At that time, mifepristone had already been approved for use in numerous countries, including the United Kingdom, Sweden and France. Based on comments from the FDA, the NDA was amended and supplemented over the course of four years.

16. Mifeprex is the only medication in the United States that has received FDA approval for marketing for the purpose of inducing abortion in the first trimester. Because Mifeprex created a new, non-surgical, option for women seeking first-trimester abortions, it met the FDA's definition of an "unmet need" and was given a priority review.

17. The drug's initial sponsor was the Population Council, a nonprofit organization dedicated to improving reproductive health worldwide. Sponsorship was ultimately transferred to Danco Laboratories, LLC, which was retained by the Population Council to manufacture mifepristone for the U.S. market.

18. The key safety and efficacy data contained in the Mifeprex NDA consisted of three clinical trials, two conducted in France and one conducted in the United States. Those trials studied a particular dosage and administration regimen for mifepristone-misoprostol consisting

of the oral ingestion of 600 milligrams of mifepristone followed two days later by the oral ingestion of 400 micrograms of misoprostol.

19. On September 28, 2000, the FDA approved the NDA for mifepristone and issued a drug approval letter to the Population Council, after determining that the drug met the applicable standards for safety and effectiveness, manufacturing and controls, and labeling. As is generally the case with respect to NDAs, the FDA did not test protocols or conduct clinical trials for mifepristone before approving the NDA. The FDA does not authorize protocols for use of approved drugs and accordingly did not authorize any protocol for use of Mifeprex.

20. The FDA's approval of mifepristone was granted pursuant to the restricted distribution provision of the FDA's Subpart H regulations, which enables the FDA to impose and enforce restrictions on the way a drug manufacturer distributes the drug. The FDA does not impose restrictions on physicians. The drug approval letter issued to the Population Council sets forth the restrictions imposed on the manufacturer with respect to distribution of mifepristone, including a set of physician qualifications. As a result of those restrictions, Danco Laboratories, LLC, may not distribute mifepristone to a physician unless the physician executes a Prescriber's Agreement stating that he or she possesses the necessary qualifications and will adhere to the other requirements set forth in the drug approval letter.

21. The Mifeprex sponsor's NDA also included a proposed label for mifepristone. The FDA reviewed the label and suggested revisions to the drug sponsor. The drug sponsor made revisions and the FDA subsequently approved what became the Final Printed Labeling ("FPL") for mifepristone. The FDA approved substantive changes to the FPL in 2004, 2005 and 2009.

22. The FPL for Mifeprex consists of four parts: Prescribing Information, Medication Guide; Patient Agreement, and Prescriber's Agreement. The Prescribing Information part of the

FPL contains Dosage and Administration information, which reflects the regimen used during the clinical trials. The Medication Guide section of the Mifeprex FPL is intended for consumers. Although it is publicly available online, the Prescribing Information section is intended for physicians, in their role as "learned intermediaries" who interpret the information for patients.

23. I have reviewed Oklahoma House Bill 1970. I know of no document that would fit the definition of a "drug label" in section A(2). There is no "protocol tested and authorized by" the FDA because, as discussed above, the FDA does not test or authorize protocols. There is no protocol "agreed upon" by the drug manufacturer, because the FDA does not require or restrict any particular protocol for use of FDA-approved drugs. Similarly, there is no "FDA authorization" of a drug, because the FDA reviews information presented by the drug manufacturer and approves labeling of a drug for marketing in the United States. I do not know of any document called "final printed labeling instructions." The FPL is not an FDA document; it is an FDA-*approved* document created and owned by the drug manufacturer. Finally, there is no document that "delineates how a drug is to be used according to the FDA approval," because the FDA does not dictate how a drug is to be used. The FPL describes the dosage and administration for the use presented to the FDA in a drug's NDA, but it in no way limits how a drug can be used.

Oversight and Monitoring of Mifeprex

24. Following the approval of mifepristone for marketing in the United States, the FDA, through the Center for Drug Evaluation and Research, has remained vigilant in its regulatory oversight of mifepristone.

25. The FDA regulations describe adverse drug experience reporting requirements. For manufacturers of approved drugs, these requirements are described at 21 CFR 314.80. That

regulation requires manufacturers to report adverse drug experiences that are both serious and unexpected. The FDA does not require physicians to report adverse reactions, but it encourages voluntary reporting by patients, consumers or healthcare professionals of any serious adverse events related to medications and other FDA approved products at any point after using the medication or product. http://www.fda.gov/Safety/Medwatch/HowToReport/default.htm.

26. Along with the regulations, the FDA provides several "Guidance to Industry" documents clarifying what, when and where to report post-marketing adverse events. In the United States, adverse events are compiled by the FDA in the Adverse Event Reporting System, which is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drugs. Adverse event reports received are reviewed by (1) the same team in the Office of New Drugs in the Center for Drug Evaluation and Research that did the New Drug Application evaluation and approval process for the specific drug about which reports are received, the members of which develop expertise related to the medication that is an important part of post-marketing monitoring; and (2) a team from the Office of Drug Safety.

27. Along with individual adverse event reports, the drug sponsor is responsible under 21 CFR 314.81 for submitting periodic safety update reports that include a description and analysis of adverse events as well as updated information from clinical trials, published literature reports, risk/benefit summaries, and any proposed changes to the product's labeling.

28. Serious adverse event reports associated with mifepristone, like those associated with any other medication, are carefully analyzed and thoroughly investigated to figure out whether there is a relationship between the drug and the event and, if so, the nature of the relationship, as well as to figure out how to prevent similar events in the future.

29. Since the approval of Mifeprex in 2000, FDA has been informed of eight deaths in the United States due to serious infections following medication abortion with mifepristone and misoprostol. The deaths resulted from toxic shock syndrome. Seven cases were found to involve infection with bacteria known as *Clostridium sordellii* and one case involved infection with *Clostridium perfringens*. Eight previous U.S. cases of fatal shock due to *Clostridium sordellii*, primarily after childbirth, have been reported in the obstetrical literature.

30. *Clostridium sordellii* and *Clostridium perfringens* are anaerobic bacteria that in very rare cases can produce toxins that are rapidly fatal. Rare infections with *C. sordellii* can occur following childbirth (both by vaginal delivery and by caesarean section) and spontaneous abortion (miscarriage), as well as following medication abortions. *C. sordellii* infections can also occur rarely with pelvic, abdominal, or orthopedic surgery, and deep skin infections.

31. On May 11, 2006, the FDA, Centers for Disease Control and Prevention, and National Institutes of Health held a joint meeting in which experts came together to better understand reports of morbidity and mortality associated with Clostridial infections. The consensus among experts was that the rare cases of Clostridial infection and death reported in mifepristone users are, at this time, not explained by a simple drug-based association. The presentations and discussions made it clear that these infections are occurring in various pregnancy-related conditions and not only post-abortion settings.

32. The FDA has concluded that no causal relationship has been established between the use of mifepristone and misoprostol and the occurrence of Clostridial infections. The Mifeprex FPL states unequivocally that "[n]o causal relationship … has been established."

33. Cases of severe infection following the use of mifepristone are so rare that the FDA does not recommend use of preventative antibiotics. Based on current data, the risks associated with such antibiotics outweigh the risks associated with mifepristone.

34. Many FDA-approved medications are associated with higher risks of morbidity and mortality than the risks associated with mifepristone.

35. Many FDA-approved medications have been the subject of public health advisories and have boxed warnings on their labels.

36. Anti-depressants, including Paxil and others, increase the risk of suicidal thinking and behavior in children, adolescents, and young adults. The FDA issued a public health advisory on October 15, 2004 about that risk. The FPL for Paxil contains a FDA-imposed boxed warning explaining the risks, and recommending monitoring and close observation of patients who use the medication.

37. Non-steroidal anti-inflammatories ("NSAIDs") like Celebrex, Motrin, and Advil, which are indicated for the treatment of arthritis and menstrual pain, increase the risks of heart attack, stroke, and serious gastrointestinal adverse events such as bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. The FDA issued a public health advisory on April 7, 2005, about these risks. The FPL for Celebrex contains a FDA-imposed boxed warning explaining the risks and recommending close monitoring of patients who use the medication.

Executed: January 25, 2012

Lisa D. Rarick, MD

LISA D. RARICK, M.D.

Exhibit A

June 2011

CURRICULUM VITAE

LISA D. RARICK, M.D.
RAR Consulting, LLC
Reproductive Health and Regulatory Affairs Consultant

PERSONAL DATA

Birth Date/Place:	February 5, 1960. Santa Monica, California
Address:	8017 Glenbrook Road Bethesda, MD 20814
Office Phone/Fax:	(301) 652-7080
Email:	Rarick215@verizon.net

EDUCATION/TRAINING

July 1977-June 1978	University of California, Riverside
July 1978-June 1980	Pacific Union College Angwin, California
July 1980-June 1984	Loma Linda University School of Medicine Loma Linda, California B.S. and M.D., June 1984
July 1984-June 1988	Resident Dept of Obstetrics and Gynecology Georgetown University School of Medicine Washington, D.C.
July 1987-June 1988	Administrative Chief Resident Dept of Ob/Gyn Georgetown University School of Medicine Washington, D.C.

APPOINTMENTS

July 1988-Sept. 1989	Instructor, Dept of Ob/Gyn Georgetown University School of Medicine
Dec. 1988-Nov. 1995	Medical Officer Division of Metabolism and Endocrine Drug Products CDER, FDA Sample Review Assignments: Gonadotropin Releasing Hormones for women (Agonists and Antagonists) Norplant and other implantable contraceptives Transdermal contraceptives Vaginal contraceptives Dopamine receptor agonists Oral Contraceptives Non-surgical sterilization Intrauterine Devices (IUDs) Drugs for Premenstrual Syndrome Anti-sperm vaccines Vaginal hormone replacement therapy
Sept. 1989-Feb. 1993	Member, Columbia Hospital for Women Physician Group
Sept. 1993-June 1996	Volunteer, Zaccheaus Free Clinic, Washington, D.C.
Nov. 1995-June.1996	Acting Deputy Director Division of Metabolism and Endocrine Drug Products CDER Served as Medical Officer group leader and as Deputy to the Division Director in the field of Reproductive and Urologic Drug Products
June 1996-Dec. 1999	Director Division of Reproductive and Urologic Drug Products CDER Was responsible for review, approval and policy for all reproductive and urologic health drugs
Dec. 1999-Nov. 2000	Deputy Director Office of Drug Evaluation 2 CDER Served as Deputy Office Director for Office with responsibility for Pulmonary, Allergy, Endocrine, Metabolic, Anesthesia, Critical Care and Addiction Drug Products

Nov. 2000-July 2002	Associate Director for Quality Assurance, Director, Review Standards Staff Office of the Center Director CDER Headed team with the mission to advance CDER-wide high priority initiatives, and lead Office for good review practice development and risk management strategic planning
July 2002-July 2003	Medical Officer Office of Women's Health Office of the Commissioner, FDA Facilitated Agency work for improving health of women, including promotion and analysis of women in clinical trials, efforts to understand and improve health during and after pregnancy, pregnancy prevention strategies, menopausal hormone therapy, HIV prevention and issues related to aging
July 2003-Present	Consultant, Reproductive Health and Regulatory Affairs

LICENSURE/CERTIFICATION

D.C. License Number: 16656, issued June 17, 1987

Maryland License Number: D0060729, issued July 31, 2003

Diplomate of the National Board of Medical Examiners: March 1985

Board Certification: American Board of Obstetrics and Gynecology: Certified December 1990; Recertified 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010

COMMITTEE ACTIVITIES

Nov. 1989-1996	FDA Liaison to American College of Obstetricians and Gynecologists Committee on Gynecologic Practice
June 1990-1996	FDA Liaison to the Technical Advisory Committee to Contraceptive Research and Development (CONRAD)
Oct.1992-1996	FDA Liaison to the International Committee for Contraception Research (Population Council)
Fall 1992-June 1995	Medication Error Subcommittee of the Drug Nomenclature Committee, FDA
June 1993-June 1995	Member, Women's Health Subcommittee of the CDER Medical Policy Coordinating Committee

Jan. 1995-July 1995	Chair, Medication Errors Response Subcommittee of the CDER Medical Policy Coordinating Committee
Spring 1994-2002	Member, CDER Good Review Practices Steering Committee
July 1995-2002	Chair, Track XI, Good Review Practices Core Committee member, several subcommittees of GRP Track XI, including reviewer education, orientation, mentoring, newsletter, scientific rounds improvement, etc.
Spring 1994-2003	FDA clinical topic lead, Multi disciplinary subgroup (M3) of the International Conference for Harmonization
Apr. 1996-1998	Chair, FDA Pregnancy Labeling Taskforce
Nov. 1998-2003	Member, FDA Pregnancy Labeling Taskforce
May 1996-2003	Subcommittee chair (pregnancy issues), Gender Effects Steering Committee
May 1996-2002	Liaison to USP re: products used in Obstetrics and Gynecology
Dec. 1995-2002	Member of taskforce addressing class labeling and labeling change policies

PROFESSIONAL SOCIETIES

Sept. 1991-Present	Fellow, American College of Obstetricians and Gynecologists (ACOG)
July 1988-1998	Member, Washington Gynecological Society
1994-1996	Secretary, Washington Gynecological Society
Mar. 1991-2003	Member, FDA-ACOG Special Interest Group
1990-1999	Member, Federal Physicians Association
1991	Vice President, Federal Physicians Association
1992-1995	Officer at Large, Federal Physicians Association

HONORS RECEIVED/PRESENTATIONS

"Resident of the Year," Georgetown University Division of Reproductive Endocrinology and Infertility - June 1987.

First Prize - Residents' Research Day Paper Presentation, Georgetown University Dept. of Ob/Gyn - Oct. 1987.

FDA Award of Merit for participation as member of Reviewer Education Subcommittee of Track XI, GRPs - May 1996.

FDA Award of Merit for providing outstanding leadership and management of ORM resources resulting in rapid delivery of safe, effective new drug products to the public - May 1997.

FDA Outstanding Group Recognition Award for outstanding performance in reviewing and analyzing complex scientific data and regulatory issues related to conjugated estrogens - Sept. 1997.

FDA Commendable Service Award for exemplary ability to facilitate and develop new CDER review staff through the New Reviewer Workshop - 1998.

CDER Leadership Excellence Award - Nov. 1998.

FDA Commendable Service Award for outstanding commitment and cooperation between FDA staff in handling post-marketing adverse events noted with the drug Viagra - 1998.

FDA Outstanding Service Award for excellence in revising estrogen labeling, class labeling guidance, and clinical trials guidance in rapid response to new risk data from the Women's Health Initiative - May 2003.

FDA Commissioner's Special Citation for the collective outstanding performance of the "Menopause and Hormones Information Campaign", which resulted in the launch of a national public awareness outreach campaign - May 2004.

Selected to present original paper entitled "Analysis of International Studies of Birth Weight" at the Annual District IV meeting of the American College of Obstetricians and Gynecologists, in joint conference with the Royal College of Obstetricians and Gynecologists, London, U.K. - Sept. 1989.

Gave multiple presentations and participated in meetings concerning regulatory affairs, public health issue policies, women's health, international harmonization of preclinical requirements to support human studies, Advisory Committee meetings, etc. Participated as faculty in several Pharmaceutical Education and Research Institute, Inc. (PERI) and Drug Information Association (DIA) courses - 1996-2007.

PUBLISHING ACTIVITIES

Rarick, LD, Shangold, MM and Ahmed, S. Cervical mucus and serum estradiol as predictors of response to progestin challenge. Fertility and Sterility, Aug. 1990.

Marshall, LW, RR Bridges, JF English, GL Lipkin, RB Miller, LD Rarick, NJ Shotwell, AH Wiseman. Incidence of post operative infections in patients undergoing abdominal hysterectomies. Abstract #S5 Infection Control and Hospital Epidemiology, Oct. 1992. Presented at the American Society of Hospital Epidemiologists, Baltimore, Maryland, Apr. 1992.

Rarick, L and L Yin, Vaginal contraceptive drugs and devices: regulatory requirements. Chapter, Barrier Contraceptives: Current Status and Future Prospects, Editors, C. Mauck, et al., Wiley-Liss, Inc., 1994.

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Rarick, Lisa D, Proceedings of The Third International Conference on Harmonisation, Data To Support Inclusion of Special Populations, pp. 345-347. Editors, P.F. D Arcy and D.W.G. Harron, International Federation of Pharmaceutical Manufacturers, IFPMA, 1996.

L Potter, J Trussell, L Rarick, New England Journal of Medicine, Letter to the Editor, Emergency Postcoital Contraception, vol 338, no. 7., February 12, 1998.

Review and Presenter—New Frontiers in Contraceptive Research: A Blueprint for Action. Institute of Medicine of the National Academy of Sciences, The National Academics Press, 2004.

Reviewer – Review of the HIVNET 012 Perinatal HIV Prevention Study. Institute of Medicine of the National Academy of Sciences, The National Academies Press, 2005.

Rarick, L, Contraception, United States regulatory considerations for intrauterine progestins for hormone replacement therapy, vol. 5, issue 6 (supplement), S140-S143, June 2007.

Exhibit B

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FDA Drug Bulletin

New Angina Drugs
Sucralfate Approved for Duodenal Ulcer
Ritodrine Update
Use of Approved Drugs for Unlabeled Indications
Hepatitis B Vaccine for Use in Selected Populations
Advice on Limiting Intake of Bonemeal
Bendectin PPI Available
Class I Recalls

New Angina Drugs

Two calcium channel blockers, nifedipine and verapamil, have been approved for treatment of vasospastic and classical effort-associated angina. These drugs are also referred to as "calcium entry blockers" or "calcium antagonists."

Drugs of this pharmacologic class have some common properties but also important differences in clinical use.

Agents inhibit transmembrane movement extracellular calcium into cardiovascular smooth muscle, and in isolated tissues, negative inotropic effects, depressed sino-atrial and atrio-ventricular (AV) node function and vasodilation. At clinical doses in humans, however, the vascular effects are usually predominant, causing reduced peripheral vascular resistance and lower blood pressure and preventing or reversing coronary spasm. The effects on cardiac tissues are usually less prominent, probably because of afterload reduction and reflex sympathetic responses to vasodilation. In patients with normal cardiac function not on other negatively inotropic drugs, the negative inotropic effects of the drugs are not usually manifested.

In some cases, however, heart failure can be induced or worsened, and particular care must be paid to concomitant use of calcium channel blockers with beta blockers and to use in patients with aortic stenosis, where vasodilation would not be expected to produce significant afterload reduction.

Effects on AV and SA node function are also not prominent *in vivo* with nifedipine, although they can occur with verapamil.

Effectiveness

Verapamil, but not nifedipine, is an effective agent intravenously in interrupting supraventricular tachycardia and slowing the heart rate in atrial fibrillation.

Both drugs are effective in angina due to vasospasm and in chronic stable angina. Current labeling for nifedipine recommends it for use in stable angina only in patients "who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents." This restriction is based on the limited long-term evidence of safety and effective-

more than 1 of every 350 patients were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

No long-term studies have been carried out and there is no recognized reason for long-term use of sucralfate. Specifically, it is not known whether sucralfate can prevent ulcer recurrence. Long-term studies will be needed to assess the possibility of adverse effects associated with long-term use, e.g., effects on absorption of fat-soluble vitamins.

The recommended adult dosage is 1 g four times a day on an empty stomach. Antacids may be prescribed as needed for relief of pain but should not be taken within 30 minutes before or after administration of sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been confirmed by X-ray or endoscopy.

Ritodrine Update

Since the approval of ritodrine (Yutopar) for use in premature labor (see November 1980 and July 1981 *Drug Bulletins*), FDA has been monitoring several areas of concern about the drug's known cardiovascular effects. In light of a number of adverse reaction reports, the labeling of ritodrine has been updated to warn about:

- the need to monitor the patient's state of hydration;
- the possibility of pulmonary edema with or without the concomitant use of corticosteroids, many cases of which seem to be related to overhydration;
- the possible unmasking of occult cardiac disease, the first sign of which may be chest pain.

Ritodrine, a beta$_2$-sympathomimetic drug, may be useful in preterm labor in pregnancies of at least 20 weeks gestation when contraindications have been ruled out.

However, in pregnancies of more than 32 weeks, physicians should carefully weigh the risks and benefits before administering the drug.

When gestational age is in doubt, intrauterine growth retardation should be considered in the differential diagnosis of preterm labor. Among low birth weight infants, about 9 percent may be growth retarded for gestational age. Prolongation of labor beyond term will not correct the growth retardation of these babies.

Initial administration of ritodrine is intravenous. To minimize the risk of hypotension, the patient should be maintained in the left lateral position during infusion and careful attention should be given to her state of hydration. The amount of i.v. fluids administered should be monitored to avoid either circulatory fluid overload (overhydration) or inadequate hydration. An excess sodium load should be avoided in hydrating the patient.[1]

The boxed warning for ritodrine has been amended to read:

> Maternal pulmonary edema has been reported in patients treated with Yutopar, sometimes after delivery. While occurring infrequently, it has occurred more often when patients were treated concomitantly with corticosteroids. Maternal death from this condition has been reported with or without corticosteroids given concomitantly with drugs of this class.
>
> Patients so treated must be closely monitored in the hospital. The patient's state of hydration should be carefully monitored. (See Dosage and Administration.) If pulmonary edema develops during administration, the drug should be discontinued. Edema should be managed by conventional means.
>
> Because cardiovascular responses are common and more pronounced during intravenous administration of Yutopar, cardiovascular effects, including maternal pulse rate and blood pressure and fetal heart rate, should be closely monitored. Observe for premonitory or actual maternal signs and symptoms of pulmonary edema. A persistent high tachycardia (over 140 beats per minute) and/or persistent tachypnea (respiratory rate over 20 per minute) may be signs of impending pulmonary edema with drugs of this class.
>
> Occult cardiac disease may be unmasked with the use of Yutopar. If the patient complains of chest pain or tightness of chest, the drug should be temporarily discontinued and an ECG should be done as soon as possible.
>
> The drug should not be administered to patients with mild to moderate preeclampsia, hypertension, or diabetes unless the attending physician considers that the benefits clearly outweigh the risks.

References

1. Philipsen T, et al.: Pulmonary edema following ritodrine-saline infusion in premature labor. *Obstet Gynec* 1981; 58(3): 304-7.

Use of Approved Drugs for Unlabeled Indications

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which FDA has approved. These are commonly referred to as "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

Hepatitis B Vaccine for Use in Selected Populations

An inactivated hepatitis B vaccine (Heptavax-B) has been licensed for use in the United States. It is intended for use in populations at high risk of acquiring hepatitis B, one of three known types of viral hepatitis. (The others are hepatitis A and non-A non-B hepatitis.)

The vaccine is the first to be made from human blood. Noninfectious antigen is purified from the plasma of asymptomatic human carriers of hepatitis B. After a series of chemical treatments, followed by the addition of alum adjuvant, the vaccine is administered in three intramuscular injections over a 6-month period.

Vaccination is not intended for the general population, but is recommended for persons older than 3 months of age who are at increased risk of hepatitis B virus infection. These persons will include health care workers, institutionalized patients, laboratory workers, hemodialysis staff and patients, family contacts of carriers, some military personnel, and persons with numerous sexual partners.

There continues to be a dialogue among government agencies, industry, and the medical community about use of the vaccine in selected high-risk groups. The Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control (CDC), with assistance from representatives of FDA, the National Institutes of Health, and the medical community, has met several times to discuss specifically which population groups should receive this vaccine. The ACIP will meet once more in May of this year to draft final guidelines for use of this vaccine.

Efficacy

In clinical trials, 85 to 96 percent of persons receiving three doses of either 20 mg or 40 mg of vaccine were immune to infection. The duration of protection is presently unknown. However, in clinical trials, vaccine-induced antibodies, shown to provide protection against infection, persisted for at least 24 months in those receiving all three doses and will probably last for at least 5 years. After this time, a booster may be necessary to maintain immunity.

Side effects have been mainly local, mild, and transitory.

Availability

Due to the complexity of the methods used for producing the vaccine, it will be summer or fall of 1982 before the product is generally available from Merck, Sharp & Dohme. This manufacturer can supply complete physician information.

Advice on Limiting Intake of Bonemeal

Due to the unknown but often substantial lead content of individual samples of bonemeal and dolomite, FDA advises practitioners that these substances should be used as little as possible in infants, young children, and pregnant or lactating women.

Bonemeal is used primarily as calcium and/or phosphorus supplements. Bonemeal supplements are usually composed of finely crushed, processed bone and are packaged in powder, capsule, tablet, or wafer form. The source of bone is usually cattle but sometimes also horses. Bone marrow may also be added to this product. All bonemeal products contain lead which originates primarily from the diet of the animals from which the bone is taken. Bone serves as a repository for lead in the body and, in general, the older the animal the more lead in its bones.

Dolomite is a mineral deposit, consisting of calcium-magnesium carbonate with traces of other elements, including lead. Dolomite is used as a calcium and magnesium supplement and, like bonemeal, may be purchased in powder, capsule, tablet, or wafer form.

While a large portion of the small amounts of dietary lead ingested by humans is excreted, some is deposited in the mineral fabric of bone and some goes into soft tissue. Infants and children tend to absorb lead more efficiently than adults. When it is consumed in excess, lead may produce toxic reactions including central nervous system damage, anemia, and abdominal pain. As in animals, the accumulation of lead in human bone increases with age. Additionally, studies with

Exhibit C

Guidance for Industry

IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2004
Clinical Medical

Revision 1

Guidance for Industry

IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer

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1401 Rockville Pike, Rockville, MD 20852-1448
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Clinical Medical

Revision 1

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Contains Nonbinding Recommendations

Guidance for Industry[1] IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors in deciding whether a study of marketed drugs or biological products for treating cancer falls within the exemption under § 312.2(b)(1) (21 CFR 312.2(b)(1)) from the general requirement to submit an investigational new drug application (IND). The guidance discusses the Agency's current thinking on when studies of marketed cancer products are exempt from IND regulation based on a risk assessment. The Agency hopes that clarifying its policy will help sponsors identify which studies are exempt, thus saving them from submitting unnecessary IND applications.

This guidance revises the guidance of the same title published in September 2003. In the September 2003 version, the Agency's final statement was that it believed that most randomized studies of a size that could support a labeling supplement would likely ***not*** be exempt from IND regulation under § 312.2(b)(1)(i), (ii). This is because they would be intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising. Experience has shown that this interpretation was formulated too broadly and inappropriately referred to size alone. The Agency has decided to revise this guidance by removing that statement (the last sentence in section V.B). Whether a study could support a change in labeling is a complex determination, based on study design, size, and other factors.

[1] This guidance has been prepared by the Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) and by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Generally, regulations in part 312 (21 CFR part 312) require sponsors who wish to study a drug or biological product in humans to submit an IND to the Agency.[2] However, these regulations also provide for the exemption of some studies from the requirement to submit an IND if they meet certain criteria. Each year, many INDs for cancer drugs are submitted that contain studies that the Agency determines are exempt. This guidance is intended to help applicants identify which studies may be exempt.

A. Regulations

Regulations in § 312.2(b)(1) provide for the exemption of some studies for some drugs from IND regulations if the studies meet the following five criteria:

1. The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.

2. The study is not intended to support a significant change in the advertising for the product.

3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that *significantly increases the risks* (or decreases the acceptability of the risks) associated with the use of the drug product.

4. The study is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in parts 56 and 50 (21 CFR parts 56 and 50).

5. The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).

Requirements 1, 2, 4, and 5 are not directly related to the specific protocol submitted, and their interpretation is similar for oncologic and nononcologic therapies. Requirement 3 is protocol related and has special meaning in the oncology therapy setting, particularly with respect to doses above the labeled dose, use with other treatments, and use in different populations.

[2] Part 312 applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

In the preamble to the IND regulations, which published in the *Federal Register* on March 19, 1987, the Agency explained that the exemption was not necessarily intended to tie the investigator to the doses and routes of administration and patient population described in the approved labeling, but to permit deviations from the approved labeling to the extent that such changes are supported by the scientific literature and generally known clinical experience. The Agency recognizes that a considerable amount of professional judgment is exercised in determining whether the planned investigation significantly increases the risk associated with the use of the drug. FDA maintains that "because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption."[3]

B. 1996 Agency Cancer Initiative

In 1996, as part of the President's National Performance Review, the Agency launched its *Reinventing the Regulation of Cancer Drugs* initiative with the goal of accelerating the approval of and expanding patient access to cancer drugs.[4] As part of this initiative, the Agency explained that many sponsor-investigators were submitting INDs for exploratory studies for so-called off-label indications for two reasons: (1) IRBs incorrectly believe an IND is required, or (2) the pharmaceutical manufacturer agrees to provide a drug free of charge, but mistakenly concludes that the FDA will view this as promotional activity. With the intent of clarifying the Agency's policy and decreasing the number of unnecessary submissions, the Agency emphasized that it would no longer accept INDs considered exempt under § 312.2(b)(1). (See § 312.2(b)(4).) Furthermore, FDA stated that providing a drug for study would not, in and of itself, be viewed as a promotional activity if the manufacturer or distributor provides the product for a physician-initiated, bona fide clinical investigation. The Agency explained that it is the responsibility of the investigator to determine whether an IND is necessary.

Despite the Agency's attempts to clarify its policy on IND exemptions, many cancer drug IND applications that the Agency determines are exempt from IND regulation are still being submitted unnecessarily. From 1997 to 1999, a majority of investigator IND submissions for marketed cancer drugs were considered exempt (204, 205, and 140 applications in 1997, 1998, and 1999, respectively).

III. RISK/BENEFIT ANALYSIS IN THE PRACTICE OF ONCOLOGY

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[3] New Drug, Antibiotic, and Biologic Drug Product Regulations, *Federal Register*, March 19, 1987, Vol. 52, Nr. 53, p. 8802.

[4] *Reinventing the Regulation of Cancer Drugs – Accelerating Approval and Expanding Access* (March 1996), CBER, Office of Communication, Training, and Manufacturer Assistance, Voice Information System at 1-800-835-4709 or 301-827-1800, document ID number 0281. Available on the Internet at http://www.fda.gov/cber/genadmin/reincanc.htm

As noted above, a critical question in determining whether a study is exempt involves criterion 3 in the exemption regulations (§ 312.2(b)(1)(iii)): The investigation may not *significantly increase the risk* associated with use of a drug product. The question of increased risk is determined by assessing the deviation in the planned investigation from the use described in the approved label. In oncology, modifications of labeled dosing recommendations are common and occur as part of oncologists' clinical practice. As outlined below, oncologists are familiar with evaluating the risk of off-label dosing regimens for cancer drug and biological products.

- Treatment with cancer drugs may be associated with significant risk from known toxicity. Because effectiveness is often related to dose, a dose close to the *maximal tolerated dose* is often selected for studies of cancer drugs. This same dose usually becomes the recommended dose in labeling when the new cancer drug is approved with the knowledge that the dose may be altered if it is not tolerated by a patient. Because it is not generally possible to have maximal efficacy in a population without inducing toxicity in some patients, it is not uncommon to observe severe or even lethal side effects from cancer drugs in some patients. In general, these circumstances mean that the toxicity, even potentially lethal toxicity, of cancer drugs is described in approved labeling.

- Off-label therapy with cancer drugs is common in practice. When there is no established therapy for a cancer, or stage of cancer, it is common for oncologists to try different regimens or combinations of established drugs. A 1996 GAO report (*Prescription Drugs, Implications of Drug Labeling and Off-Label Use*) showed that there was substantial off-label use in situations where satisfactory treatment was not available, and lower rates of off-label use when there was an effective therapy. In their daily practice, many oncologists treat cancer patients with regimens that include off-label use of drugs. They evaluate the published data and past clinical experience to assess the risk of such treatments. Such treatment of individual patients with approved drugs within their clinical practice does not require an IND (§ 312.2(d)).

- In many cases, as discussed in the examples in section V below, drug administration to patients with similar off-label regimens in the context of an investigation seems to involve no increased risk to patients, and an investigator could conclude that such a study would not *significantly increase the risk* associated with the labeled use of a drug product and the study could be conducted without an IND. Oversight by an IRB and informed consent in compliance with parts 56 and 50, respectively, would be required as usual (§ 312.2(b)(1)(iv)). On request, FDA will advise on the applicability of the IND exemption to a planned clinical investigation (§ 312.2(e)).

IV. DETERMINING APPLICATION STATUS

A. Agency Determination

As explained in FDA's 1996 cancer initiative and the IND exemption regulation, FDA will not accept applications for clinical studies that it determines to be exempt from the requirement for an IND (§ 312.2(b)(4)). Although § 312.2(b)(1) does not require a submission for a determination of exempt status, whenever an IND application is submitted, FDA staff perform an initial limited review of the application to determine whether the study is exempt. The protocol-related criterion FDA considers in assessing exemption is: The investigation may not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product (§ 312.2(b)(1)(iii)). Thus, when determining if the risk is significantly increased, FDA staff examine the parts of the protocol that concern dose, schedule, route of administration, and patient population. If the Agency's initial limited review determines that a study protocol is exempt from the requirement for an IND, the Agency performs no further review of the application. A letter is sent to the sponsor giving notice of the exemption.

B. Investigator Determination

When determining if an IND needs to be submitted to study marketed drugs for treating cancer, investigators must apply the exemption criteria listed in § 312.2(b)(1)(i-v) in light of the discussion in this guidance. Planned studies may be considered exempt from the requirements of an IND if the studies involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a patient population with cancer and the following conditions apply:

- The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
- The studies are not intended to support a significant change in the advertising for the product.
- Investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no *significant increase in the risk associated with the use of the drug product.*
- The studies are to be conducted in compliance with IRB and informed consent regulations, pursuant to parts 50 and 56.
- The studies will not be used to promote unapproved indications, in compliance with § 312.7.

V. EXAMPLES OF STUDIES

The following examples of studies are being provided to illustrate the Agency's current thinking on the types of studies that the Agency considers to be exempt from IND regulation based on a risk assessment.

A. Studies That Generally Are Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely be exempt from IND regulation based on protocol-related issues.

1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in the marketed drug labeling are usually exempt. An exception may exist when standard therapy in the population to be studied is very effective (e.g., is associated with a survival benefit); in that case, use of another regimen may expose patients to the risk of receiving an ineffective therapy and an IND would be necessary.

2. Phase 1 oncology trials of marketed drugs may be considered exempt if such therapy is appropriate for the patient population (i.e., if patients have residual cancer) and if there is no effective therapy (i.e., therapy producing cure or a documented increase in survival) that the patients have not yet received. It remains the investigator's responsibility to use starting doses that appear safe based on approved labeling or detailed literature reports, use incremental changes in dose or schedule, and carefully evaluate toxicity prior to dose escalation.

3. The study of new combinations of drugs would not ordinarily constitute a significant risk if these combinations have been described in the professional medical literature. Even when the regimen described in the literature does not use exactly the doses planned for study, incremental differences in doses from those described in the literature would not normally pose a significant risk and would not require an IND.

   Because of the danger of synergistic toxicity (i.e., enhanced effects from the combination) occurring with a new drug combination, if there are no data from the literature on its safety, the initial study of a new drug combination should ordinarily be performed under an IND. Synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent. If it is determined that synergistic toxicity is likely, animal studies should be considered for determining a safe starting dose for the drug combination in humans.

4. Studies of new routes or schedules of administration not described in the approved labeling are generally exempt if there is sufficient clinical experience described in the literature documenting safety to determine that treatment is safe. On the other hand, initial experience with a new route of administration should be based on studies in animals, and an IND should be submitted.

5. Studies of high-dose therapy in cancer patients are likely to be considered exempt if the studies use adequately evaluated regimens that appear to have an acceptable therapeutic ratio for the population being studied. Similarly, phase 1 studies involving incremental changes from such well-described regimens are generally exempt.

B. Studies That Generally Are Not Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely *not* be exempt from IND regulation because of protocol-related issues.

1. Studies of cytotoxic drugs are normally not exempt in patients for whom cytotoxic therapy would not be considered standard therapy and would require special justification. Any use of cytotoxic agents in nonmalignant disease (e.g., rheumatoid arthritis, multiple sclerosis) would, most likely, be considered to alter the acceptability of the risk of the agent.

2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to remove cancer) are likely not exempt for the following reasons:

   - If the population studied has a low risk of cancer recurring after surgery, treatment with any toxic therapy may indicate a significantly increased risk.

   - If standard adjuvant therapy is available and produces a survival benefit, substitution of new therapy for standard therapy poses a significant risk that the new therapy will not produce the same survival benefit.

   - If adjuvant trials are properly designed, they usually will be able to demonstrate whether the new therapy is safe and effective, and such results may lead to a marketing application. As discussed earlier, under regulations at § 312.2(b)(1), all investigations intended to support marketing of a new product indication, significant change in product labeling, or a significant change in the advertising for a product require an IND. During FDA review of INDs intended to support marketing applications, the Agency will provide feedback about the acceptability of trial design for this purpose.

3. Studies involving substitution of a new agent of unproven activity are generally not exempt in settings where standard therapy provides a cure or increase in survival. For instance, in the first-line treatment of testicular cancer, ovarian cancer, breast cancer, leukemia, and lymphoma, studies of new agents without proven efficacy would likely not be exempt. In this case, the critical judgment is whether it is ethical to withhold standard therapy while testing a new agent.

4. Studies are generally not exempt in settings where animal studies should be conducted to determine a safe starting dose or schedule.

   For example:

- Initial studies of a marketed drug given by a new route of administration are likely not exempt.

- Unless adequately described in the literature, initial studies of new drug combinations should usually be performed under an IND because of the possible occurrence of synergistic toxicity. As noted earlier, synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent.

- Initial studies in humans of changes in the schedule of drug administration should generally be submitted in an IND. Some drugs have demonstrated significantly greater toxicity when given by an alternative schedule (e.g., methotrexate demonstrates much more hematologic toxicity when given by prolonged administration compared to intermittent administration).

- Initial studies of drugs intended to be chemosensitizers, radiosensitizers, or resistance modulators should generally be submitted in an IND. Animal studies should be used to estimate the effect of the modulator on toxicity and to allow estimation of a safe starting dose in humans.

5. Studies intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising are not exempt (§ 312.2(b)(1)(i), (ii)).

Appendix 3

United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

GAO-08-751

August 2008

GAO
Accountability·Integrity·Reliability

Highlights

Highlights of GAO-08-751, a report to congressional requesters

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

Why GAO Did This Study

In September 2000, the Food and Drug Administration (FDA), part of the Department of Health and Human Services (HHS), approved the drug Mifeprex for use in terminating early term pregnancy. FDA approved the drug under a provision of its Subpart H regulations, allowing it to restrict the drug's distribution to assure its safe use. Critics have questioned aspects of the Mifeprex approval process, including the reliance on historically-controlled clinical trials that compare a drug's effects on a condition to the known course of the condition rather than to another drug or placebo. Critics argued that Mifeprex does not fit within the scope of Subpart H, which applies to drugs that treat serious or life-threatening illnesses. Concerns have also been raised about FDA's oversight of the drug since approval, including the agency's response to deaths in U.S. women who had taken the drug.

In this report GAO (1) describes FDA's approval of Mifeprex, including the evidence considered and the restrictions placed on its distribution; (2) compares the Mifeprex approval process to the approval processes for other Subpart H restricted drugs; and (3) compares FDA's postmarket oversight of Mifeprex to its oversight of other Subpart H restricted drugs. GAO reviewed FDA regulations, policies, and records pertaining to its approval and oversight of Mifeprex and the eight other Subpart H restricted drugs. In addition, GAO interviewed FDA officials and external stakeholders.

To view the full product, including the scope and methodology, click on GAO-08-751. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA approved Mifeprex after evaluating the sponsor's initial and revised new drug application through three review cycles. In the first cycle, FDA concluded that the available data supported the safety and efficacy of Mifeprex and that, because the course of pregnancy was well-documented and the effects of the drug were self-evident, the use of historical controls was consistent with FDA regulations. FDA also concluded that before the drug could be approved, the sponsor needed to provide final data from an ongoing U.S. trial, and more detail on restricting the drug's distribution. In the second cycle, FDA concluded that while the U.S. trial data confirmed the drug's safety and efficacy, the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In the final review, FDA concluded that termination of unwanted pregnancy is a serious condition and imposing restrictions under Subpart H was necessary. FDA approved Mifeprex, but required that the sponsor commit to conduct two postmarketing studies, imposed several distribution restrictions intended to ensure that only qualified physicians prescribe the drug, and required that patients attest to understanding the treatment's potential complications.

The approval process for Mifeprex was consistent with the processes for the other Subpart H restricted drugs, although the details of FDA's approval depended on the unique risks and benefits of each drug. Common elements of the approval processes included that FDA needed to evaluate potential limitations in key clinical data (Mifeprex and six of the other drugs), did not approve the drugs in the first review cycle (Mifeprex and five others), and imposed similar types of distribution restrictions on Mifeprex and the other drugs, though the specific details of the restrictions varied across the drugs.

FDA's postmarket oversight of Mifeprex has been consistent with its oversight of other Subpart H restricted drugs. To oversee compliance with distribution restrictions, FDA has reviewed data from all sponsors and conducted inspections for Mifeprex and two other drugs. To oversee compliance with postmarketing study commitments, FDA has relied on required updates from sponsors and found unfulfilled commitments for most drugs, including Mifeprex. To oversee compliance with adverse event reporting requirements, FDA has evaluated data in sponsors' reports and, for Mifeprex and seven other drugs, has conducted inspections that revealed deficiencies for most of these drugs, including Mifeprex. Lastly, FDA has taken similar steps to oversee postmarket safety across the drugs, such as analyzing adverse events. For Mifeprex, FDA investigated the deaths of six U.S. women who developed a severe infection after taking the drug and concluded that the evidence did not establish a causal relationship between Mifeprex and the infections. Finally, FDA has taken similar actions to address emerging safety concerns across the drugs, such as changing labeling.

HHS reviewed a draft of this report and informed GAO that it did not have comments.

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Abbreviations

AERS	Adverse Event Reporting System
CDC	Centers for Disease Control and Prevention
ENL	erythema nodosum leprosum
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus / acquired immune deficiency syndrome
NDA	new drug application
REMS	risk evaluation and mitigation strategy
SGE	special government employee

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GAO
Accountability * Integrity * Reliability
United States Government Accountability Office
Washington, DC 20548

August 7, 2008

The Honorable Michael B. Enzi
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Jim DeMint
United States Senate

The Honorable Roscoe G. Bartlett
House of Representatives

In September 2000, the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) granted marketing approval to the prescription drug Mifeprex (mifepristone) for the medical termination of early term pregnancy.[1] It remains the only drug approved in the United States for this purpose. FDA approved the drug under a provision of the agency's Subpart H regulations that allows FDA to restrict the distribution or use of a drug in order to assure its safe use.[2] Under this provision FDA can require, as it did for Mifeprex, that distribution be restricted to certain health care providers with specific training or experience. Since the drug's approval, more than 900,000 women are estimated to have taken Mifeprex in the United States.

[1]Mifeprex is the trade name for the mifepristone product marketed in the United States. Mifepristone is the name of the underlying drug substance. Mifepristone is also sometimes called "RU-486," a reference to the name the drug had during laboratory testing.

[2]Subpart H of FDA's drug approval regulations—titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses"—applies to drugs that are intended to treat serious or life-threatening illnesses and provide a meaningful therapeutic benefit to patients over existing treatments. The regulations contain two approval provisions. One provides a process through which FDA may restrict the distribution or use of a drug to assure its safe use. The other provides FDA with flexibilities that allow the agency to accelerate the approval process for certain drugs on the basis of clinical trial endpoints that are considered reasonably likely to predict clinical benefit. See 21 C.F.R. §§ 314.500-560 (2007).

Before a drug can be marketed in the United States, the drug sponsor must submit a new drug application (NDA) to FDA containing data demonstrating the safety and efficacy of the drug.[3] FDA reviews the NDA to determine whether the drug's benefits outweigh its risks.[4] Once FDA completes its review, the agency issues an action letter in which it either approves the drug as safe and effective for its intended use (approval letter), informs the sponsor that the drug is likely to be approved once the deficiencies FDA has identified are resolved (approvable letter), or indicates that approval cannot be obtained without substantial additional information (not approvable letter).[5] If FDA issues an approvable or not approvable letter, a subsequent review cycle can begin once the sponsor has addressed the issues FDA identified. FDA may require, as a condition of approval, that a sponsor agree to restrict the drug's distribution under the agency's Subpart H regulations.[6]

Critics have raised concerns and questions regarding several aspects of FDA's approval process for Mifeprex. For example, questions have been raised about the reliance on data from historically controlled clinical trials—trials that compare a drug's effects on a condition within the study population to the known course of that same condition in patients or

[3]A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

[4]FDA also reviews supplemental NDAs, which sponsors submit to support proposed changes to a drug's label, a new dosage or strength of the drug, a new patient population or intended use, or changes to the way the drug is manufactured after a drug has an approved NDA.

[5]FDA issued a final rule on July 10, 2008, amending its drug approval regulations. The final rule, among other things, discontinues FDA's use of approvable letters and not approvable letters. Instead, in the event that FDA determines it will not approve an application in its current form, the agency will send applicants a "complete response letter" to indicate that the review cycle for an application is complete and to describe the specific deficiencies the agency identified in the application. The amended regulations are effective on August 11, 2008. See 73 Fed. Reg. 39588-89 (July 10, 2008).

[6]21 C.F.R. § 314.520 (2007). From 1992—the year that the regulations were promulgated—through February 2007, nine drugs, including Mifeprex, had either an NDA or supplemental NDA approved under this restricted distribution provision. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may determine that a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks. The REMS provisions of FDAAA went into effect on March 25, 2008. As part of a REMS, FDA can require "elements to assure safe use," which include restrictions similar to those that can be required under Subpart H regulations. 21 U.S.C. § 355-1(a), (e), (f); Pub. L. No. 110-85, §§ 901, 909(a), 121 Stat. 823, 922, 926-38, 950.

populations that were not part of the trial—to support the safety and efficacy of Mifeprex.[7] FDA regulations allow for the use of such historical controls when the course of the condition in question is well-documented within a comparable population and the effect of the drug is apparent. Questions have also been raised about whether Mifeprex fit within the scope of Subpart H regulations, which apply to drugs that are intended to treat a serious or life-threatening illness. Critics have argued that unwanted pregnancy should not be considered a serious or life-threatening illness. They have also questioned whether FDA's use of Subpart H regulations was consistent with its use of the regulations to approve other drugs.

Additionally, concerns have been raised about FDA's postmarket oversight of Mifeprex, including its efforts to ensure the sponsor's compliance with conditions of approval as well as the actions the agency has taken in response to reported adverse events.[8] For approved drugs, FDA oversees sponsors' compliance with applicable reporting requirements, distribution restrictions, and other conditions of approval.[9] FDA also monitors the drugs' postmarket safety and efficacy. In the case of Mifeprex, six U.S. women have died from severe bacterial infection after taking the drug, raising questions about its safety. Some have questioned FDA's conclusion—which it discussed at a May 2006 congressional hearing—that the available evidence had not established a causal relationship between Mifeprex and the infections.

You asked us to review FDA's approval of Mifeprex and its oversight of the drug since approval. In this report we (1) examine FDA's approach to approving Mifeprex, including the types of evidence considered and the

[7]21 C.F.R. § 314.126(b)(2)(v) (2007). In contrast, clinical trials that use concurrent controls demonstrate the safety and efficacy of a drug by comparing its effects on patients in a treatment group to the effects of a different treatment—such as another drug or a placebo—on patients in a control group within the same study population.

[8]The term postmarket refers to activities occurring after a drug has been approved for marketing. FDA uses the term adverse drug event to refer to any untoward medical event associated with the use of a drug in humans.

[9]FDA regulations require sponsors of approved drugs to submit various postmarket safety reports. See 21 C.F.R. §§ 314.80, 314.81 (2007). Additionally, sponsors of approved drugs must report to FDA annually on the progress of any postmarket studies required by FDA or agreed to by the sponsor. 21 U.S.C. § 356b; 21 C.F.R. § 314.81(b)(2)(vii) (2007). FDA uses such postmarket studies to gather additional information about a drug's safety, efficacy, or use once it is marketed.

restrictions placed on its distribution and use; (2) compare the approval process for Mifeprex to the approval processes for other drugs approved under the restricted distribution provision of Subpart H; and (3) compare FDA's oversight of the use of Mifeprex since its approval to the agency's oversight of the other drugs approved under the restricted distribution provision of Subpart H.

To examine FDA's approval of Mifeprex, we reviewed relevant laws, regulations, policies, and guidance. We reviewed FDA records including an archive of documents pertaining to the approval of Mifeprex.[10] We also reviewed documentation from an FDA advisory committee meeting,[11] testimony statements and the related transcript, FDA responses to congressional requests, an August 2002 citizen's petition and responses from outside organizations, and other documentation pertaining to FDA's approval of Mifeprex. We interviewed FDA officials and external stakeholders who had access to technical information or had conducted analyses pertaining to Mifeprex that were not available through FDA. These included a representative of the sponsor of the Mifeprex application and its licensee,[12] the American College of Obstetricians and Gynecologists and the American Association of Pro Life Obstetricians and Gynecologists.

To compare the approval process for Mifeprex to those of other drugs, we reviewed FDA documentation pertaining to FDA's approval of the other eight drugs that the agency had approved under the restricted distribution

[10]In response to a Freedom of Information Act request, FDA posted certain documents pertaining to its approval of Mifeprex on the agency's Web site (see http://www.fda.gov/cder/archives/mifepristone/default.htm). The documents, which total over 9,000 pages, include a range of sometimes redacted material such as handwritten notes or email communications, communications between the drug sponsor and FDA, meeting minutes, copies of international labeling, and study protocols.

[11]FDA may convene an advisory committee to obtain advice from scientific experts and representatives of the public regarding a drug. FDA requests advice from advisory committees on a variety of matters, including aspects of drug applications and postmarket safety concerns for drug products. The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making. Although the committees provide recommendations to the agency, final decisions are made by FDA.

[12]The Population Council, a non-profit organization involved in reproductive health and population issues, sponsored the Mifeprex application. During the NDA review process, the Population Council contracted with Danco Laboratories, L.L.C. to serve as its licensee with responsibility for commercial manufacturing and marketing of the drug. Following the drug's approval, the Population Council transferred ownership of the Mifeprex NDA to Danco.

provision of Subpart H as of February 2007.[13] Specifically, we examined key documents related to FDA's internal review and approval processes as well as documentation from advisory committee meetings in order to identify commonalities and differences in FDA's process across the nine Subpart H restricted drugs, including Mifeprex. In our examination we focused on issues that had arisen during FDA's review of Mifeprex to determine whether similar issues had arisen in FDA's review of the other drugs, and how FDA had addressed those issues for the other drugs.

To compare FDA's oversight of the use of Mifeprex since approval to the agency's oversight of the other Subpart H restricted drugs, we reviewed relevant regulations and FDA guidance. We also examined FDA documentation on the agency's oversight of sponsors' compliance with distribution restrictions, postmarketing study commitments, and adverse event reporting requirements for the nine Subpart H restricted drugs. In addition, we reviewed FDA's process for evaluating and responding to postmarket data on adverse events for each drug. Lastly, we interviewed FDA officials and staff who are responsible for postmarket oversight of these drugs. We conducted our work from February 2007 through August 2008 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.

Results in Brief

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of its Subpart H regulations after examining the NDA through three review cycles. In its first review, FDA concluded that the available evidence supported the safety and efficacy of Mifeprex. This conclusion was based in part on FDA's determination that because the course of pregnancy was well-documented and the effects of the treatment were self-evident, the reliance on historical controls in three key clinical trials—two conducted in France and one ongoing in the United States—was appropriate and consistent with FDA regulations. FDA issued an approvable letter in September 1996 concluding that the sponsor needed

[13]We initiated our work in February 2007. In June 2007, FDA approved one additional drug—Letairis—under the restricted distribution provision of Subpart H. This drug was not included in our review.

to provide additional information, such as the final data from the U.S. trial and a detailed plan to restrict the drug's distribution, before an approval decision could be made. The second review cycle began when the sponsor submitted a complete response to this letter. FDA issued a second approvable letter in February 2000 after concluding that the new data confirmed the safety and efficacy of Mifeprex for the U.S. market but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In its final review, FDA deliberated about the distribution restrictions and conditions of use needed to assure the safe use of the drug. FDA concluded that termination of an unwanted pregnancy is a serious condition and that the drug can allow patients to avoid a surgical procedure and therefore Mifeprex fit within the scope of Subpart H. FDA further concluded that the drug could only be used safely if distribution was limited to qualified physicians. The sponsor argued that the drug did not treat a serious condition and that because they had voluntarily agreed to the restrictions FDA had requested, it was neither appropriate nor necessary to impose the restrictions under Subpart H. However, the sponsor eventually acquiesced to FDA's requirement that approval be under Subpart H. After FDA concluded that the sponsor had adequately revised its distribution plan and addressed the remaining issues identified in FDA's reviews, it approved the Mifeprex NDA under Subpart H with several restrictions. These included requiring that prescribing physicians attest to possessing specific skills, agree to fully discuss the treatment with patients, and agree to report certain adverse events to the sponsor; that the drug be distributed directly to physicians by an authorized distributor; and that patients attest to fully understanding the treatment and its potential complications. The drug was also approved subject to the sponsor's commitment to conduct two postmarket studies related to patient outcomes.

The approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs, but the details of FDA's approval process for each drug depended on the drug's unique risks and benefits. One common element across the approval processes for seven of the drugs, including Mifeprex, was that FDA needed to evaluate potential limitations—such as lack of concurrent controls or small sample sizes—in key clinical trials supporting the NDA. For some of these drugs other than Mifeprex, FDA concluded that there were weaknesses in the data submitted in the NDA that needed to be addressed. Another common element for six of the drugs, including Mifeprex, was that FDA issued at least one prior action letter before ultimately approving the drug for marketing under Subpart H. Additionally, the types of distribution restrictions that FDA imposed on Mifeprex were similar to

those the agency imposed on the other drugs, though the details of the restrictions varied depending on the drug. Lastly, eight of the drugs, including Mifeprex, were approved with two or more postmarketing study commitments, each with one or more commitments related to adverse events or patient outcomes of interest.

FDA's postmarket oversight of Mifeprex has been consistent with the agency's postmarket oversight of the other Subpart H restricted drugs. To oversee the drug sponsors' compliance with distribution restrictions, FDA has relied on data submitted by sponsors for all of the drugs. For three of the drugs, one of them Mifeprex, FDA has also completed inspections of the sponsor or its distributors. To oversee compliance with postmarketing study commitments, FDA has relied on updates in required reports from sponsors. Most of the drugs, including Mifeprex, have at least one study commitment that remains unfulfilled. To oversee compliance with adverse event reporting requirements, FDA has relied on sponsors' reports for all of the drugs and has also conducted inspections of the sponsor or its manufacturers for eight of them. FDA has cited the sponsors of seven of the drugs, including Mifeprex, for adverse event reporting deficiencies. To oversee the postmarket safety of all of the Subpart H restricted drugs, FDA has routinely conducted reviews of adverse event reports to monitor for safety concerns. In the case of Mifeprex, FDA investigated the deaths of six U.S. women who developed a fatal infection following treatment with Mifeprex for medical abortion. FDA has determined that in all six of the deaths, the women used a Mifeprex treatment regimen that has not been approved by FDA. Based on its investigations, FDA has concluded that a causal relationship between the use of Mifeprex and the fatal infections has not been established. FDA has also monitored other kinds of adverse events and has concluded that, with the exception of the cases of fatal infection, reported serious adverse events associated with Mifeprex have been within or below the ranges it expected. Additionally, for Mifeprex and the other drugs, FDA has taken similar actions—such as issuing warnings and requesting changes to the product labeling—to communicate safety information to consumers and health care providers.

HHS reviewed a draft of this report and informed us that it did not have general comments. In addition, HHS provided technical comments which we incorporated as appropriate.

Background

The Mifeprex NDA provided for the use of Mifeprex, in combination with another drug, for the medical termination of pregnancy. The treatment regimen described in the NDA involved taking Mifeprex orally, and then taking the drug misoprostol orally 2 days later unless termination of the pregnancy had already occurred.[14] Patients return for a follow-up visit with their prescribing physician 2 weeks later to ensure that the termination of the pregnancy has been completed. The treatment regimen 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.

At the time that the drug sponsor submitted the Mifeprex NDA, in March 1996, mifepristone had already been approved in multiple countries. The drug was first approved for the medical termination of pregnancy in France and China in 1988.[15] It was approved subsequently in the United Kingdom in 1991, in Sweden in 1992, and various other European countries throughout the 1990s. In general, the treatment regimens approved in these countries were similar to those studied in the Mifeprex NDA, though in some cases the specific drug used in combination with mifepristone was different.

FDA Application Review Process

FDA reviews drug applications to determine whether they provide sufficient evidence to demonstrate that a drug is safe and effective for the proposed use, including whether the benefits of the drug outweigh its risks. FDA's formal process for new drug approval begins after a drug sponsor submits an application, typically following a long period of research and development. During a preliminary review, FDA determines whether the application is sufficiently complete to be reviewed and if so, designates it for either standard or priority review, depending on the

[14]Misoprostol is one of several drugs that had been studied in combination with mifepristone for the medical termination of pregnancy because they have been shown to induce uterine contractions. However, it is approved for marketing in the United States for a different indicated use.

[15]The company that discovered mifepristone and manufactured it for marketing in France—Roussel Uclaf—did not want to produce the drug for the U.S. market. Instead, the U.S. sponsor retained a contract manufacturer. For a more detailed discussion of the history of the development of mifepristone for the U.S. market, see: Congressional Research Service, *Abortion: Termination of Early Pregnancy with RU-486 (Mifepristone)*, (Washington, D.C.: 2001).

therapeutic potential of the drug.[16] The agency then assigns a team of reviewers—including medical officers, chemists, statisticians, microbiologists, pharmacologists, and other experts—within the relevant FDA review division. This review team, which is usually led by a medical officer, conducts a comprehensive evaluation of the clinical and non-clinical information in the application including the safety and efficacy data for the drug, the design and quality of the studies used to support the application, and the proposed labeling for the drug and also reviews the results of inspections of the facilities where the drug is manufactured.[17] The review team compiles the results of its analyses and recommends either an approval, approvable, or not approvable action.

FDA managers, usually including the review team's supervisor and senior management within the applicable review division, determine what action to take on an application, based on the recommendations of the review team. These managers examine the review team's analysis and individually decide whether to concur with the recommendation. The final decision on the action the agency should take is usually, but not always, made by the director of the applicable review division. In some cases, actions must be reviewed and agreed to by the relevant FDA office.

This review process may span several cycles. For those applications not approved during the first review cycle—both approvable and not approvable—the second FDA review cycle begins once the sponsor submits an amendment to the application providing responses to the deficiencies FDA identified in its previous review. These amendments often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The responsible review team reviews the information provided by the sponsor, conducts any additional analyses that are required, reviews the results of any additional inspections that have been conducted, and again recommends either an approval, approvable, or not approvable action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the

[16]FDA may grant priority review status when it determines that a drug may provide significant benefits in the treatment, diagnosis, or prevention of a disease as compared to marketed drugs or non-drug therapies, such as surgery, or provide a treatment where no adequate therapy exists.

[17]The non-clinical data in an NDA pertains to, for example a drug's chemistry, manufacturing, and controls as well as its toxicology and pharmacology.

review team and makes its decision on the action to take on the application.

Restricting Drug Distribution and Subpart H Regulations

To address concerns FDA identifies regarding the safe use of a drug, the agency may condition approval by requiring that the sponsor agree to restrict the drug's distribution. FDA has established restricted distribution programs for approved drugs primarily by requiring that a drug's approval be under the restricted distribution provision of Subpart H regulations. According to the scope of the regulations, Subpart H applies to new drugs that "have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments" for the condition.[18] FDA may approve a drug under the restricted distribution provision of these regulations if it meets these criteria and the agency concludes that the drug is effective but can be safely used only if distribution or use is restricted. For example, FDA may require that distribution of a drug be limited to certain facilities or physicians with special training.

As of February 2007, nine drugs—Actiq, Accutane, Lotronex, Mifeprex, Plenaxis, Revlimid, Thalomid, Tracleer, and Xyrem—had either an NDA or supplemental NDA approved under the restricted distribution provision of Subpart H.[19] For each of the drugs, either during the application review process or based on postmarket data, FDA identified concerns about the safe use of the drug that led the agency to apply Subpart H. The drugs were approved to treat a range of conditions, such as breakthrough cancer pain, specific symptoms of narcolepsy, and severe acne.

FDA has also required that drug sponsors agree to restrict the distribution of drugs without imposing Subpart H. Clozaril, Tikosyn, and Trovan are three examples of drugs that have restricted distribution programs that were imposed outside of Subpart H. (See app. I for a table describing drugs FDA has approved with restricted distribution programs and the conditions they are intended to treat). While Clozaril was first approved in

[18]21 C.F.R. § 314.500 (2007).

[19]21 C.F.R. § 314.520 (2007). The sponsor for Plenaxis—approved in 2003 for the palliative care of certain patients with advanced prostate cancer—withdrew the product from the market in 2006. Additionally, three generic versions of Accutane have been approved for marketing under this restricted distribution provision.

1989, FDA imposed distribution restrictions on both Tikosyn and Trovan after Subpart H regulations had been promulgated.

A second approval provision of Subpart H provides FDA with flexibilities that allow the agency to accelerate the approval process for drugs that provide meaningful therapeutic benefits over alternatives for serious or life-threatening illnesses.[20] Specifically, under the provision, FDA may approve a drug on the basis of clinical trials establishing that the drug has an effect on a surrogate endpoint—such as weight gain or reduced occurrence of infections in patients with HIV—that is reasonably likely to predict a clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.[21] This allows FDA to approve a drug before measures of effectiveness that would usually be required for approval are available. However, under this approval provision, drug sponsors are ordinarily required to conduct postmarket studies to confirm and further describe the drug's clinical benefit. As of February 2007, FDA had used this provision to approve 52 drugs, most of which are intended to treat HIV/AIDS or various cancers.

FDA's Role in Postmarket Oversight

Because some risks may not become known until after a drug's approval and use in a wider segment of the population, FDA has a range of postmarket oversight responsibilities once a drug is approved for marketing in the United States. FDA's postmarket oversight responsibilities include assessing sponsors' compliance with requirements for a given drug, such as postmarketing study commitments, adverse event reporting, and restricted distribution requirements. In addition, FDA monitors reported adverse events to assess the postmarket safety of approved drugs and may take action if it develops a concern about a drug's safety.

With regard to postmarketing study commitments, FDA oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report to FDA annually on their progress in meeting the

[20]See 21 C.F.R. § 314.510 (2007).

[21]According to FDA, although some surrogate endpoints are recognized as well-established and have long been a basis for approval (such as change in blood pressure or cholesterol), accelerated approval regulations allow reliance on a "surrogate endpoint that, while 'reasonably likely' to predict clinical benefit, is not so well-established as the surrogates ordinarily used as bases of approval in the past." 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

commitments. FDA requires that sponsors report on the status of these studies in an annual report that also includes updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.[22] FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA also oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with an approved drug.[23] Sponsors must provide in periodic reports (quarterly for the first 3 years after approval and annually thereafter) a narrative summary and analysis of adverse event information. For adverse events that are considered both serious and unexpected,[24] sponsors are required to submit a report—known as a "Postmarketing 15-day Alert Report"—to FDA within 15 calendar days from the time the sponsor was informed of the event. To assess sponsors' compliance with these adverse event reporting requirements, FDA reviews sponsors' reports and conducts inspections of the sponsors' reporting policies and procedures.

For drugs approved under the restricted distribution provision of Subpart H, FDA oversees sponsors' compliance with the restrictions placed on the drugs' distribution or use. To assess compliance with restrictions, FDA reviews information such as summaries of sponsors' distribution programs in annual reports and in some cases separate reports required by the agency to provide details and updates on distribution programs. In addition, FDA may conduct inspections of a sponsor's corporate headquarters, manufacturing sites, or contractors, such as specialty distributors, to evaluate whether distribution policies and procedures comply with the approved restrictions for a given drug. If FDA identifies deficiencies during an inspection, it may issue a formal citation—known as a Form FDA 483. In addition, FDA may communicate less serious findings as written or oral "observations" or "recommendations."[25]

[22]See 21 C.F.R. § 314.81 (2007).

[23]See 21 C.F.R. § 314.80 (2007).

[24]Unexpected events are those that are not included in the current labeling for a drug.

[25]FDA uses the same reporting scheme—noting citations, observations, or recommendations— for its inspections to assess sponsor compliance with adverse event reporting.

To monitor postmarket safety of approved drugs, FDA reviews clinical literature, routinely evaluates the available data on reported adverse events, and conducts investigations of the nature and patterns of these events. FDA compiles data from sponsor's reports on adverse events, along with data from voluntary reports submitted to the MedWatch program, in its Adverse Event Reporting System (AERS) database.[26] FDA safety evaluators analyze data from AERS and in the clinical literature to detect signs of potential safety concerns. These evaluations may reveal the need for further studies of a drug or may result in FDA action to ensure the safety of the drug.[27]

If FDA identifies problems with a sponsor's compliance with agency requirements or identifies postmarket safety concerns, the agency can take a range of actions to address the concern and communicate safety information to healthcare providers and the public. For example, FDA may revise the restrictions on a drug's distribution, request changes to a drug's labeling, issue patient advisories or public health alerts, or request that a sponsor issue letters to health care providers or pharmacists to alert them to safety concerns. FDA may also issue a regulatory letter citing violations of laws or regulations. Typically, FDA issues a Warning letter for violations that may lead FDA to pursue further enforcement action if not corrected or issues an untitled letter for violations that do not meet this threshold. FDA also has the authority to withdraw a drug's marketing approval for safety-related and other reasons,[28] although it rarely does so. Additionally,

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

[27]GAO has previously reported on and made recommendations regarding FDA's postmarket oversight of approved drugs. See GAO, *Drug Safety: Improvements Needed in FDA's Postmarket Decision-making and Oversight Process*. GAO-06-402. (Washington, D.C.: Mar. 31, 2006).

[28]21 U.S.C. § 355(e).

Subpart H regulations establish an expedited process for withdrawing a drug's marketing approval, in certain circumstances.[29]

FDA Approved Mifeprex under the Subpart H Restricted Distribution Provision After Concluding That Clinical Evidence Supported Its Safety and Efficacy

FDA approved Mifeprex after three review cycles. In its initial review, FDA concluded that reliance on historical controls in three key clinical trials was appropriate and consistent with FDA regulations and that the available data supported the safety and efficacy of the drug. In an approvable letter, FDA notified the sponsor that it needed to provide additional data and more detail on its proposal to restrict the drug's distribution before an approval decision could be made. A second review cycle began when the sponsor submitted data responding to this letter. The agency issued a second approvable letter after finding that new data confirmed Mifeprex's safety and efficacy but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. FDA further concluded that the drug was a candidate for approval under Subpart H. In the final review cycle, FDA concluded that the sponsor's revised distribution plan and other revisions were sufficient to address FDA's comments. FDA also concluded that Mifeprex met the scope of Subpart H and that approval under the restricted distribution provision of Subpart H was necessary to ensure that only qualified physicians prescribed the drug. On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H with several restrictions and two postmarketing study commitments. (See table 1 for a timeline of key events in the Mifeprex approval process.)

[29]Under Subpart H regulations, FDA may withdraw a drug's marketing approval after providing for a hearing, in the following circumstances; (1) a postmarketing clinical study fails to verify clinical benefit; (2) the sponsor fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) the sponsor fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use. 21 C.F.R. § 314.530 (2007).

Table 1: Timeline of Key Events in FDA's Approval of Mifeprex

Date	Event
First review cycle	
March 1996	The sponsor submitted a new drug application (NDA) for the use of Mifeprex in combination with the drug misoprostol for the medical termination of intrauterine pregnancy.
July 1996	FDA Reproductive Health Drugs Advisory Committee meeting.
September 1996	FDA issued an approvable letter listing issues that the sponsor needed to address before the application could be approved.
Second review cycle	
August 1999	After delays securing a manufacturer, the sponsor completed its responses to FDA's 1996 approvable letter.
February 2000	FDA issued a second approvable letter, listing issues that the sponsor needed to address prior to approval.
Third review cycle	
March 2000	The sponsor completes its responses to FDA's second approvable letter.
September 2000	FDA approved Mifeprex under the restricted distribution provision of Subpart H.
November 2000	Distribution of Mifeprex began in the United States.

Source: GAO analysis of FDA and drug sponsor data.

FDA's Initial Review Cycle and Approvable Action (March to September 1996)

FDA's initial review began when the drug sponsor submitted the Mifeprex NDA in March 1996. After conducting a preliminary review of the NDA, FDA designated the application for priority review, establishing a goal that the agency would issue an action letter within 6 months. FDA's rationale for the designation was that as the first drug that would be approved for its particular indication, Mifeprex was a therapeutic advance because women using the drug could potentially avoid the risks of surgery and anesthesia involved in a surgical termination of a pregnancy.

FDA assigned a team of reviewers within the Division of Reproductive and Urologic Drug Products to review the evidence in the Mifeprex NDA. The key safety and efficacy data in the NDA consisted of three historically controlled clinical trials, two conducted in France and one conducted in the United States. These trials studied the Mifeprex treatment regimen—mifepristone in combination with misoprostol—in a total of more than 4,000 women. At the time the NDA was submitted, the French trials were complete and the U.S. trial was ongoing. As a result, during the first review cycle, the review team analyzed the complete safety and efficacy data from the French clinical trials, but only summary data on serious adverse events

from the U.S. clinical trial. FDA reviewers also considered results from other trials conducted in Europe from 1983 through 1996 in which mifepristone was studied either alone or in combination with misoprostol or similar drugs. In addition, the review team considered safety information from extensive postmarketing experience in Europe, including a postmarket safety database containing information on women who had used mifepristone. Lastly, the review team considered the non-clinical data in the application, including data on the drug's chemistry and manufacturing.

In its review of the Mifeprex data, FDA reviewers determined that the reliance on historical controls in the key clinical trials was appropriate and consistent with FDA regulation. According to FDA, historical control designs can make it more difficult to evaluate which effects can be attributed to the drug being studied.[30] However, FDA regulations list historical controls as an acceptable type of control when the natural history of the condition being treated is well-documented and when the effects of the drug are self-evident.[31] In the case of the Mifeprex NDA, FDA determined that the historically controlled trials provided substantial evidence of safety and efficacy because the outcomes of women taking the Mifeprex regimen were compared with the well-documented data on the natural course of pregnancy, including rates of miscarriage, and the effect of the drug—termination of a pregnancy—was obvious.[32]

To assist the review team in its assessment of Mifeprex, FDA convened the Reproductive Health Drugs Advisory Committee in July 1996 and asked the members to examine the data and vote on their conclusions regarding the drug's safety and efficacy. Six of the eight voting members voted, with

[30]See FDA, *Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Tials* (Rockville, Md.: May 2001).

[31]21 C.F.R. § 314.126(b)(2)(v) (2007). The regulation also states that studies that are "adequate and well-controlled" provide the primary basis for determining whether there is "substantial evidence" in support of the claims of effectiveness for new drugs. Among other things, an adequate and well-controlled study provides sufficient details of study design, conduct, and analysis to allow critical evaluation, and the design must permit a valid comparison with a control to provide a quantitative assessment of the drug's effect.

[32]FDA has cited examples of other drugs that have relied upon historical controls. According to FDA, for contraceptives the effect of the drug can be compared to the well-documented rate of pregnancy in sexually active women between the ages of 15 and 35 in the absence of contraception. For example, FDA approved the contraceptive drug products Lybrel, Implanon, Yaz, and NuvaRing on the basis of historically controlled clinical trials.

two abstentions, that the available evidence demonstrated that the benefits of the regimen outweighed its risks for the proposed indication in the United States. However, the members agreed unanimously that FDA should provide the final safety and efficacy data from the U.S. clinical trial for their review. The advisory committee also discussed the basic elements of a voluntary restricted distribution system proposed by the drug's sponsor, which would require that Mifeprex be distributed directly to physicians, that prescribing physicians meet certain training requirements, and that patients meet certain conditions before receiving the drug. The advisory committee voted unanimously that they agreed with the concept of restricting distribution of the drug but had reservations about how the proposed system would assure that physicians had adequate credentials. The members recommended that the sponsor conduct postmarket studies to address six unanswered questions about the treatment regimen and the distribution system. The members also provided extensive comments on the draft labeling proposed by the sponsor.

The FDA review team concluded that the NDA was approvable, based on its assessment of the clinical and non-clinical data and the input from the advisory committee. The medical officer leading the review team concluded that the available clinical data indicated "that medical abortion can be safely delivered in a wide variety of United States settings." The data from the French trials showed the treatment to be roughly 95 percent effective at terminating pregnancy through 49 days gestation. The data from the French clinical trials also showed that almost all patients experienced some side effects—such as uterine cramping and bleeding—most of which were expected based on the way the drug works. Though serious adverse events were considered rare, some women experienced bleeding that required medical intervention, and approximately 0.2 percent of patients required transfusion. The medical officer concluded that the preliminary U.S. data on adverse events did not appear to differ significantly from the French trials.[33]

[33]The medical officer noted that it was only possible to make general comparisons across these events because definitions and reporting requirements were different in the two countries. Additionally, while the sponsor had not yet completed its analysis of the safety and efficacy data from the U.S. clinical trial, information from the studies was forwarded to the sponsor weekly. The medical officer concluded, based on preliminary examination of this information, that the final results of the U.S. trials were likely to be similar to the results of the French trials.

In September 1996, FDA issued an approvable letter for the use of Mifeprex in combination with the drug misoprostol for the termination of intrauterine pregnancy up to 49 days gestation. In memos documenting concurrence with the review team, and in the approvable letter itself, FDA management outlined the clinical and non-clinical issues the sponsor needed to address prior to approval. First, the full data from the U.S. clinical trial were needed to establish safety and efficacy of the Mifeprex regimen in the U.S. health care setting. Second, FDA agreed with the sponsor's proposal to limit the drug's distribution, but the sponsor had not yet submitted sufficient detail on how it would be implemented to allow for the plan to be fully evaluated.[34] Third, the drug labeling proposed by the sponsor needed to be revised to provide more information on the treatment and to address comments from the advisory committee. Fourth, the sponsor would need to commit to pursue the postmarket studies suggested by the advisory committee. Finally, the sponsor would need to address certain deficiencies in chemistry and manufacturing data identified in FDA's review.

FDA's Second Review Cycle and Approvable Action (August 1999 to February 2000)

FDA's second review cycle for the Mifeprex NDA officially began once the sponsor had completed its responses to the first approvable letter. However, these responses were delayed because of difficulties the sponsor encountered in securing a manufacturer for the drug product. In the interim, the sponsor submitted a range of data to FDA, including the final safety and efficacy results from the U.S. clinical trial, updated safety data from other trials of mifepristone and international postmarketing experience with the drug, formal revisions of the product labeling, and outstanding chemistry and manufacturing data. In August 1999, the sponsor completed its responses to the approvable letter by submitting an overview of the key principles of the restricted distribution system as well as responses to the postmarketing study commitments. At the time of this submission, the sponsor was still working with its planned distributor on the details of the restricted distribution system.

Based on the updated data, the review team recommended approval for the Mifeprex NDA once the sponsor had clarified the details of the drug's distribution, revised the drug labeling, and addressed deficiencies in the

[34]FDA management's concurrence memos noted that because the sponsor had voluntarily proposed a restricted distribution system, imposing restrictions through Subpart H regulations did not appear warranted.

chemistry and manufacturing data. The medical officer concluded that the final results from the U.S. clinical trial were acceptable and confirmed the results of the French trials that the regimen was safe and effective.[35] The medical officer concluded that the comments from the July 1996 advisory committee meeting were fully considered and, to the extent possible, implemented.[36] The medical officer also concluded that additional detail was needed to determine whether the sponsor's proposed distribution plan was sufficient. The non-clinical reviews during this review cycle—which included inspections of manufacturing facilities[37]—identified deficiencies in the drug's chemistry data and manufacturing processes that needed to be addressed, as well as sections of the drug's labeling that needed to be revised.

In January 2000, the sponsor submitted a more detailed plan describing how the proposed distribution restrictions would be implemented. The plan had three key elements. First, the Mifeprex regimen would only be administered under the supervision of qualified physicians who had agreed to provide the treatment according to several guidelines. Specifically, prescribing physicians would be required to attest to being able to accurately assess the duration of a pregnancy, diagnose an ectopic pregnancy,[38] and assure that patients have access to appropriate follow up care if needed to manage complications. The physicians would also need to agree to fully explain the procedure to each patient and obtain her

[35]The U.S. clinical trial data showed the treatment to be 92 percent effective for terminating pregnancy through 49 days gestation, which was slightly lower than the 95 percent from the French trials. Adverse event rates were also slightly higher in the U.S. trials. The medical officer attributed these differences to the relative inexperience of U.S. clinicians with the treatment. In addition, the medical officer concluded that the updated information from international studies, postmarket experience, and the published literature was consistent with the results from the U.S. and French trials.

[36]In November 1999, FDA provided advisory committee members the final results from the U.S. clinical trial for their review and comment. FDA did not receive any comments from the members on these results.

[37]The drug substance (mifepristone) in the Mifeprex product was manufactured by the Shanghai Haulian Pharmaceutical Co., Ltd., with the manufacturing facilities located in China. Initial FDA inspections found the manufacturer not in compliance with FDA's good manufacturing practice standards.

[38]Ectopic pregnancy—which occurs when a fertilized egg improperly implants outside of the uterus—is a contraindication for receiving the Mifeprex regimen. Accurate screening to ensure that patients with an ectopic pregnancy do not receive the treatment was a concern because a ruptured ectopic pregnancy is a life-threatening condition and its symptoms are similar to the side effects of the Mifeprex regimen.

signed consent, record the unique product serial number for tracking purposes, and report any serious adverse event or on-going pregnancy to the sponsor. Second, the drug would only be distributed directly to physicians after an authorized distributor had verified that the physician had registered with it and had a signed attestation on file. Third, patients would be required to meet certain conditions before receiving the drug, such as signing a patient agreement attesting to her understanding of the potential complications of the treatment.

FDA management concluded that the proposed distribution plan did not provide for adequate training and certification of prescribing physicians and needed to be revised before the NDA could be approved. In February 2000, FDA issued a second approvable letter for Mifeprex, notifying the sponsor that it needed to revise its proposed distribution plan, address deficiencies in the drug's chemistry data and manufacturing, and revise the drug's labeling. The letter also stated that FDA had considered the application under the restricted distribution provision of Subpart H and that distribution restrictions would be necessary in order to assure the safe use of the drug. The approvable letter further reminded the sponsor of its commitment to pursue postmarketing study commitments to address questions that were raised at the time of the advisory committee meeting.

FDA's Final Review Cycle and Marketing Approval for Mifeprex (March to September 2000)

In March 2000, the sponsor submitted its complete response to FDA's February 2000 approvable letter. This submission included updated safety data from ongoing trials and international postmarket experience, international product labeling, and revisions to the distribution plan. The sponsor also provided additional data and revisions—including updated chemistry and manufacturing data, a revision to the distribution plan, and revised labeling—to address comments from FDA that arose during the review cycle. The agency's review of these submissions included multiple meetings and teleconferences with the sponsor and input from a consultant who was a special government employee (SGE) and a member of the Reproductive Health Drugs Advisory Committee.[39]

[39]According to FDA, it is not uncommon for the agency to consult with members of its advisory committees who have special expertise in a particular drug under review. Generally, an SGE is defined as an officer or employee who is retained, designated, appointed, or employed by the government to perform temporary duties, with or without compensation, for not more than 130 days during any period of 365 consecutive days. 18 U.S.C. § 202(a).

During the final review cycle, FDA's deliberations—which involved a wide range of agency staff and management, including at times the Commissioner—focused on four key issues: whether prescribing physicians should be required to participate in a formal training and certification program, whether to require that approval be under Subpart H, what conditions of use should be specified, and what postmarketing study commitments would be needed to assure the safe use of the drug.

- Physician Training: In its deliberations, FDA considered requiring that physicians participate in specific training and have their qualifications certified before being allowed to prescribe Mifeprex, as opposed to relying on the sponsor's proposed system of self-attestation. However, FDA concluded that such a requirement was not necessary. FDA officials told us that the agency determined that its concern about ensuring that prescribers were adequately qualified could be addressed by requiring that the sponsor make educational materials and training programs readily available and requiring that prescribing physicians sign an agreement attesting to their qualifications. The SGE consultant agreed with this conclusion. FDA officials also told us that the agency wanted to minimize the burden that the restricted distribution program would place on providers and patients by requiring only what was necessary to address safety concerns.[40]

  In July 2000, the sponsor submitted its revised distribution plan. This plan addressed FDA's comments by providing increased emphasis in the product labeling on the educational materials and trainings available to physicians and the importance of participating in the training. The other key elements of the plan—including the specific qualifications that physicians were required to meet and agreements regarding discussing the treatment and adverse event reporting—were essentially unchanged from those the sponsor proposed in its January 2000 plan.

- Approval under Subpart H Regulations: FDA had maintained through the first two review cycles that distribution restrictions would be required for Mifeprex. However, minutes from meetings between FDA and the sponsor indicate that the agency was still considering whether it was necessary to impose those restrictions under Subpart H during the final review cycle. During the second review cycle, FDA had concluded that the restricted

[40]Subpart H regulations state that any restrictions imposed will be commensurate with the specific safety concerns presented by the drug product. 21 C.F.R. § 314.520(b) (2007).

distribution provision could be applied to Mifeprex.[41] FDA eventually concluded that it would be necessary to do so. In its documented rationale for this conclusion, FDA stated that the drug met the scope of the regulations because the termination of an unwanted pregnancy is a serious condition, and that the drug provided a meaningful therapeutic benefit over existing therapies by allowing patients to avoid the procedure required with surgical termination of pregnancy. FDA officials told us that the agency has broad discretion to determine which conditions or illnesses may be considered serious or life threatening, and that in the case of Mifeprex it considered the potential in any pregnancy for serious or life-threatening complications—such as hemorrhage—in its determination.[42] Additionally, FDA concluded that Mifeprex could only be used safely if distribution was limited to physicians who could assess the duration of a pregnancy, diagnose an ectopic pregnancy, and provide patients with access to surgical intervention if necessary.

Throughout the approval process, the sponsor was opposed to approval under Subpart H. Specifically, the sponsor argued that the drug did not fit within the scope of Subpart H because pregnancy itself is not a serious or life threatening illness. The sponsor also argued that the intent of the restricted distribution provision was to allow for restricted distribution of highly toxic or risky drugs, and that Mifeprex did not fit this description.[43] The sponsor also expressed concern that approving the drug under Subpart H could unfairly mark Mifeprex as risky and deter women from using the drug. Lastly, the sponsor held that imposing Subpart H was unnecessary because it had voluntarily committed to the distribution

[41]FDA had also noted that approving the drug under Subpart H would allow the agency to impose similar restrictions on any future generic mifepristone products approved for the same indication. The patent for Mifeprex expired in October 2004, but as of May 2008, no generic versions of mifepristone have been approved for marketing.

[42]The terms "serious" and "life-threatening" are not defined in Subpart H regulations, but were discussed in the preambles to the proposed and final rules. In its proposed rule, FDA stated that the seriousness of a disease is a matter of judgment, but generally is based on its impact on survival, day-to-day functioning, or other factors, and provided examples of conditions that could be within the scope of the regulation. FDA noted that many diseases or conditions can be serious for some populations in some or all of their phases and explicitly reserved the discretion to determine whether the regulations were applicable to a given product. See 57 Fed. Reg. 13234-5 (Apr. 15, 1992), 57 Fed. Reg. 58942, 58946 (Dec. 11, 1992); See also 21 C.F.R. §§ 312.34, 312.81 (2007), and FDA, *Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review* (Rockville, Md.: Jan. 2006).

[43]In support of its arguments about the intent of the regulations, the sponsor cited the pertinent language from preambles to the proposed and final rules. See footnote 42.

restrictions requested by FDA. However, in a September 2000 letter to FDA, the sponsor agreed to FDA's requirement that approval be under Subpart H, while noting that it still believed that applying these regulations to Mifeprex was not appropriate.

- Conditions of Use: FDA reviewed data and held multiple meetings with the sponsor regarding the specific conditions of use that should be required for Mifeprex. For example, FDA deliberated about whether it was necessary to require that prescribing physicians possess the ability to perform follow-up surgical interventions in the event that it was necessary to manage complications. The sponsor maintained that such a requirement was inconsistent with the practice of medicine, because management of incomplete miscarriages was routinely handled by referring patients to outside providers with specialized surgical or emergency care training. On this issue, FDA concluded that access to follow-up care could be ensured by requiring adequate information in the labeling and requiring that physicians attest to having made arrangements for their patients to have access to any needed surgical or emergency care. The SGE consultant agreed with FDA's conclusion. FDA disagreed with the sponsor on other suggested conditions of use. For example, the sponsor provided data to support allowing patients to self-administer the misoprostol dose at home, instead of requiring them to return to their prescribing physicians. FDA concluded that the available data did not support the safety of home use of misoprostol and that such use should not be included in the final product label. As a part of its deliberations about the conditions of use, FDA also concluded that approved labeling should include a medication guide to provide patients with information about the risks and benefits of the drug and the approved conditions of use and treatment regimen.[44]

- Postmarketing Study Commitments: In both the September 1996 and February 2000 approvable letters, FDA had reminded the sponsor of its commitment to conduct a series of six postmarket studies to address comments raised in the 1996 advisory committee meeting. FDA reviewed data and met with the sponsor during the final stages of its review to revisit these commitments in light of experience gained with the treatment regimen since the advisory committee meeting, concerns about potential infringement on the privacy of patients, and the potential resources needed to fulfill all six commitments. FDA concluded that the originally proposed commitments could be sufficiently addressed in two redesigned

[44]FDA may require that a drug be distributed with a medication guide that provides patients with information about the safe and effective use of the drug. See 21 C.F.R. pt. 208 (2007).

studies. The first was a study on the safety outcomes of a group of patients receiving the treatment under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention when necessary. The second was a surveillance study to determine the outcomes of ongoing pregnancies that were not surgically terminated after a failure of the Mifeprex regimen, including the health of any children born. FDA also concluded that the outstanding questions could be incorporated into the two postmarket studies and an audit of signed patient agreement forms.

Once the sponsor had addressed the issues that FDA raised during the third review cycle, both the review team responsible for the Mifeprex NDA and FDA management concluded that the drug should be approved. The medical officer concluded that the updated safety data did not reveal any new issues that would change the ratio of benefit-to-risk for the drug. The medical officer also reviewed revised product labeling related to the distribution of the drug. Based on these reviews, the medical officer recommended approval of the application. The non-clinical reviews during this review cycle included additional inspections of manufacturing facilities. After the sponsor had addressed several issues, including deficiencies identified in a second inspection of the drug manufacturing facilities, the non-clinical reviewers also recommended approval of the application. FDA management concurred with the recommendations of the review team that the Mifeprex NDA should be approved.

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H. The sponsor began distribution of Mifeprex in November 2000. FDA approved the drug with the two postmarketing study commitments discussed above and with several key restrictions on distribution. First, prescribing physicians must sign a prescriber's agreement attesting to possessing the training and skills needed to administer the treatment regimen, and also agreeing to provide patients with the approved medication guide. They must also attest that they will fully discuss the treatment with patients and report to the sponsor any serious adverse events or ongoing pregnancies that are not terminated after a failure of the Mifeprex regimen. Second, the drug must be distributed directly to prescribing physicians by an authorized distributor only after the distributor has verified that the physician has a signed agreement on file. Third, patients must sign a patient agreement attesting to having read, discussed, and understood the risks and potential complications of the treatment. For a more detailed list of the individual components of the restricted distribution program for Mifeprex, see

appendix II. For a copy of the approved prescriber's agreement, see appendix III.

Approval Process for Mifeprex Was Generally Consistent with That of the Other Eight Subpart H Restricted Drugs

Although each drug had unique risks and benefits, the approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs. Each of the drugs had unique risks and benefits that were specific to their indication and target populations. For some of the drugs, the safety issues that prompted FDA to apply Subpart H were similar, with the potential for causing birth defects, the potential for liver or other serious toxicities, and appropriate patient selection being the most common issues. However, there were also safe use concerns that were unique to particular drugs. For example, for Mifeprex, ensuring patient access to follow-up care was a key safety concern, while for Actiq a key concern was ensuring that children did not accidentally ingest the drug.[45] Each of the drugs represented potential advances in the treatment of their targeted condition and in two cases—Mifeprex and Xyrem—the drug was the first approved to treat that condition. (See app. I for a table including each of the Subpart H restricted drugs and their approved indications.)

One common element across the approval processes for the Subpart H restricted drugs was that for seven of the drugs, including Mifeprex, FDA needed to evaluate potential limitations in key clinical data supporting the NDA. Specifically, with the exception of Accutane and Lotronex, the drugs were approved on the basis of studies without concurrent controls or data that were limited by relatively small sample sizes or data collection issues.[46] FDA approved the Mifeprex NDA on the basis of historically controlled clinical trials that studied the drug in several thousand patients. FDA concluded that the use of historical controls was not a limitation

[45]Actiq contains the controlled substance fentanyl in a lozenge formulation intended to allow for more rapid delivery of the medication for pain management in patients who have developed a tolerance. Because of the formulation there are concerns that Actiq may be perceived by children as a lollipop.

[46]Both Accutane and Lotronex were approved under Subpart H after they had first been marketed in the United States. In the case of Lotronex, the sponsor withdrew the drug from the market in 2000 because of safety concerns. In 2002, FDA approved a supplemental NDA under Subpart H, allowing the drug to be marketed with a restricted distribution program and substantially more limited indication. For Accutane, which was originally approved for marketing in 1982, FDA approved a supplemental NDA under the restricted distribution provision of Subpart H in 2005 in order to require a more formal restricted distribution program that linked Accutane prescribing and dispensing to pregnancy testing results.

because the course of pregnancy was well-documented and the effect of the treatment was self-evident. Revlimid, Thalomid, Plenaxis, and Xyrem were also each approved on the basis of data that included at least one key clinical study that lacked a concurrent control.[47] In contrast to the Mifeprex data, FDA concluded that the lack of concurrent controls in these studies was a weakness because data on the course of the disease in a comparable population was not available to be used as a reliable historical control. For example, Thalomid was approved on the basis of clinical trial data from the published literature as well as a series of retrospective case studies for several dozen patients.[48] Additionally, five of the drugs—Actiq, Revlimid, Thalomid, Tracleer, and Xyrem—were approved on the basis of key clinical studies with relatively small sample sizes of several hundred patients or less. Finally, for Actiq, Plenaxis, Thalomid, and Xyrem, FDA identified data collection issues, such as incomplete documentation, in some of the key data sources.

Another common element was that for six of the drugs, including Mifeprex, FDA issued at least one prior action letter before ultimately approving the drug for marketing. FDA issued one approvable letter before ultimately approving Thalomid and Tracleer. Both Mifeprex and Xyrem received two approvable letters. In some cases the types of issues FDA cited—such as insufficient safety or efficacy data, the need for additional information on the restricted distribution system, or chemistry and manufacturing issues—were similar. For all four of these drugs, the adequacy of proposed distribution restrictions was a significant issue. For Xyrem, FDA's initial approvable action was also linked to the sufficiency of the data provided in the application. FDA issued not approvable letters for both Actiq and Plenaxis prior to their eventual approval. In the case of Actiq, FDA cited multiple deficiencies, such as reliance on a key clinical study with flaws and an inadequate plan for risk management. For Plenaxis, FDA initially concluded that the risks of the drug exceeded its

[47]FDA approved Plenaxis on the basis of one uncontrolled clinical trial in the indicated population—men with advanced symptomatic prostate cancer—and three concurrently-controlled clinical trials in men with less advanced prostate cancer. FDA approved Xyrem on the basis of one uncontrolled key safety trial, and two concurrently-controlled clinical trials.

[48]FDA considers such case studies to be historically controlled. In this case, the reviewing division concluded that the data were not sufficient to demonstrate the safety and efficacy of Thalomid. However, that decision was overridden by both the Director of the relevant FDA office and the Director of FDA's Center for Drug Evaluation and Research, based on their individual analyses of the available data.

benefits because of the potential for severe, systemic allergic reactions in patients.

As a result of these complexities, the approval process for the Subpart H restricted drugs was typically longer than the process for other drugs. Across the seven drugs with NDAs approved under Subpart H, an average of almost 25 months elapsed from the time that the sponsor submitted its NDA to the time FDA approved the NDA. The length of time to approval ranged from almost 9 months for Revlimid to more than 54 months for Mifeprex. In comparison, in analyses conducted for our 2006 report on new drug development, we found that it took FDA on average almost 18 months to approve NDAs submitted from 1996 through 2002.[49]

We also found that the types of distribution restrictions FDA imposed on Mifeprex were similar to those imposed on the other Subpart H restricted drugs, though the specifics of the restrictions depended on FDA's safe use concern for the drug.[50] (See table 2.) For all of the drugs except Actiq, FDA required some form of program enrollment or registration process. For example, for Mifeprex and three other drugs, FDA required that patients sign written agreements and that physicians enroll in a prescribing program and attest to their qualifications. For five of the drugs, FDA required formal registries of all prescribing physicians and patients.[51] Additionally, for seven of the drugs, FDA required that distribution be limited to authorized distributors or pharmacies.[52] And for eight of the

[49]See, GAO, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49. (Washington, D.C.: Nov. 17, 2006). In contrast, the drugs approved under the surrogate endpoint provision of Subpart H have generally been approved more rapidly than drugs approved under the restricted distribution provision of Subpart H and than drugs approved outside of Subpart H.

[50]Additionally, except for Plenaxis, FDA convened a meeting of the relevant advisory committee prior to each drug's approval under Subpart H to obtain expert input regarding the appropriate actions to address the agency's safe use concerns, including the distribution restrictions that should be required. The advisory committee meetings that FDA has held for the drugs Accutane and Lotronex occurred after each drug was first marketed in the United States, but prior to their approvals under Subpart H.

[51]FDA has used various types of registries as a mechanism to collect data on patients, providers, and others as a tool for monitoring outcomes of interest.

[52]Two of the drugs—Actiq and Xyrem—were approved as controlled substances and therefore subject to the restrictions imposed by the Controlled Substances Act. Requirements imposed under this act are enforced by the Drug Enforcement Administration and are distinct from the distribution restrictions imposed on these drugs by FDA under Subpart H. See, e.g., 21 U.S.C. § 822; 21 C.F.R. § 1301.11 (2007).

drugs, FDA required that the sponsor establish a process to ensure that dispensing or distribution of the drug was contingent on verification that physicians and others had enrolled or registered in the distribution program, or that patients had complied with certain safety measures. FDA also required that all of the sponsors implement some form of educational program for patients, prescribers, or pharmacists, though FDA did not require that prescribing physicians participate in formal training for any of the drugs. For six of the nine drugs, FDA required that the sponsor report periodically to the agency specifically on implementation of their restricted distribution programs. For seven of the drugs, FDA required that sponsors report to the agency on specific adverse events—such as fetal exposures or liver toxicity—more frequently than is required for other drugs. In the case of Mifeprex and Xyrem, at the time the drugs were approved, FDA did not require that the sponsors submit additional adverse event reports beyond those required for all approved drugs, but did require that physicians agree to report specific types of adverse events to the sponsor.

Table 2: Selected Features of Restricted Distribution Programs Imposed by FDA at Time of Approval under Subpart H

Features Required at Approval	Mifeprex (mife-pristone)	Lotronex (alosetron hydro-chloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Prenaxis (abarelix for injectable suspension)	Revlimid (lenali-domide)	Accutane (isotretinoin)
Program enrollment or registration[a]	✓	✓		✓	✓	✓	✓	✓	✓
Limited distribution channels[b]	✓			✓	✓	✓	✓	✓	✓
Dispensing or distribution contingent on verification[c]	✓	✓		✓	✓	✓	✓	✓	✓
Sponsor developed educational programs[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reporting specific to implementation of restricted distribution program		✓	✓	✓	✓		✓		✓
Additional adverse event reporting by the sponsor[e]		✓	✓	✓	✓		✓	✓	✓

Source: GAO analysis of FDA data.

[a]Program enrollment or registration requirements varied across the drugs. For Accutane, Lotronex, Mifeprex, and Plenaxis, FDA required that physicians enroll in a prescribing program and attest to their qualifications. For Accutane, Revlimid, Thalomid, Tracleer, and Xyrem, FDA required formal registries of all prescribing physicians and patients. FDA also required registration of pharmacies, wholesalers, or distributors for Thalomid, Revlimid, and Accutane.

[b]The specific limitations imposed on distribution channels varied across the drugs, and in some cases more than one limitation was required. These limitations included, for example, requiring that a drug only be distributed directly to prescribing physicians, allowing only authorized distributors or wholesalers to ship a drug, and allowing only registered or centralized pharmacies to dispense a drug.

[c]The verification mechanisms varied across the drugs. For example, for Mifeprex, an authorized distributor must verify that a physician has a signed prescriber agreement on file before distributing the drug. For Lotronex, before dispensing and drug, pharmacists must verify that prescriptions include a sticker that is only available to physicians enrolled in the prescribing program. For Accutane, Revlimid, and Thalomid, a registered pharmacy is required to confirm prescription authorizations and that patients have complied with requirements to use one or more methods of contraception before dispensing the drug.

[d]In general, sponsors were required to develop educational materials (such as patient information videos) for patients, and make educational materials and training programs readily available to prescribing physicians, pharmacists, and other groups involved in the restricted distribution program. For some of the drugs, dispensing pharmacists were required to participate in formal training. At the time of Subpart H approval, FDA required medication guides for all of the drugs except Actiq, Plenaxis, and Thalomid.

[e]Sponsors for seven of the drugs were required to submit 15-day alert reports on specific adverse events. Sponsors of four of the drugs were required to provide updates more frequently than typically required for events related to FDA's safe use concern for the drug. For Mifeprex, as part of their prescriber agreement, physicians agreed to report ongoing pregnancies, hospitalizations, transfusions, and other serious events to the sponsor. For Xyrem, FDA required that physicians agree to collect and report to the sponsor information on specific adverse events and inappropriate use of the drug.

Finally, eight of the nine Subpart H restricted drugs were approved with two or more postmarketing study commitments.[53] Each of these had at least one commitment that involved developing a postmarket study to monitor adverse events or patient outcomes of interest for that drug. The number of study commitments FDA required ranged from 2 to 10, depending on the drug. Additionally, for most of the drugs, including Mifeprex, the study protocols for the various commitments had not been finalized at the time of approval.

[53]FDA's approval of Accutane under Subpart H through a supplemental NDA did not include any postmarket study commitments.

FDA's Postmarket Oversight of Mifeprex Has Been Consistent with the Agency's Oversight of the Other Subpart H Restricted Drugs

The actions FDA has taken to oversee Mifeprex have been consistent with the actions it has taken to oversee the other Subpart H restricted drugs. FDA has relied primarily on information submitted by the sponsors of all the Subpart H restricted drugs and inspections for three of the drugs to oversee compliance with restricted distribution requirements. FDA has also relied on updates submitted by these sponsors to oversee compliance with postmarketing study commitments and has found that most have unfulfilled commitments. To oversee compliance with adverse event reporting requirements, FDA has reviewed a variety of safety information including reports submitted by the sponsors of all nine of the drugs restricted under Subpart H and has conducted inspections to evaluate compliance with reporting of adverse events for eight of the drugs. As a result, for most of the drugs, FDA has identified deficiencies in compliance with adverse event reporting requirements. To oversee reported adverse events FDA has used similar methods—such as monitoring, investigating, and addressing safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. As a result of its oversight of safety data, FDA has identified postmarket safety concerns for most of the drugs and has used a variety of methods to communicate safety information to health care providers and the public. (See table 3 for an overview of FDA's postmarket oversight of these drugs.)

Table 3: Selected Features of FDA's Oversight of Postmarket Safety for Drugs Approved under Subpart H, as of May 2008

Oversight Activities and Findings	Mifeprex (mife-pristone)	Lotronex (alosetron hydro-chloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenali-domide)	Accutane (isotretinoin)
FDA has completed inspection(s) to oversee compliance with distribution restriction requirements[a]	✓				✓	✓			
FDA has classified at least one postmarketing study commitment as unfulfilled[b]	✓	✓	✓	✓	✓		✓	✓	n/a
FDA has conducted inspection(s) to oversee compliance with adverse event reporting requirements[c]	✓	✓	✓	✓	✓	✓	✓		✓
FDA has identified a postmarket safety concern leading to communication of new safety information to public or health care providers[d]	✓	✓	✓	✓	✓	✓		✓	✓

Source: GAO analysis of FDA data.

Note: FDA provided or confirmed data on these selected features of oversight through May 2008.

[a]In May 2008, FDA officials told us that they had conducted such inspections for three additional drugs. However, the reports from those inspections were not yet available. Inspections were in addition to report review.

[b]FDA classifies unfulfilled postmarketing study commitments as ongoing, pending, delayed, released, or terminated; FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarketing study commitments and has submitted the final report for the third and final commitment.

[c]Inspections were in addition to report review conducted for all of the drugs. In the case of Revlimid, FDA inspected Celgene—the sponsor of both Revlimid and Thalomid—before Revlimid was approved in December 2005.

[4]Communication of new safety information includes activities such as changing product labeling, issuing Public Health Advisories and Safety Alerts, and distributing letters to health care providers.

To Oversee Compliance with Distribution Restrictions, FDA Relied on Information Submitted by All Drug Sponsors and Its Own Inspections for Some of the Drugs, Including Mifeprex

For all nine of the drugs that have been approved under the restricted distribution provision of Subpart H, FDA has relied mainly on information submitted by sponsors in required reports to oversee the sponsors' compliance with distribution restrictions. For six of the drugs—not including Mifeprex—FDA relied on reports specific to the drugs' restricted distribution programs.[54] The type of information provided by the sponsors in these documents included data on the operation of the restricted distribution program, such as requirements for distributors, pharmacies, prescribers, and patients participating in the program. In addition, to oversee compliance with the restricted distribution programs for most of the drugs—including Mifeprex—FDA has relied on annual reports, supplemental applications, or periodic reports for required updates on the postmarket use of the drugs, including summaries of updates to the restricted distribution program.[55]

Through the end of 2007, FDA had conducted inspections specifically to oversee sponsors' compliance with distribution restrictions for three of the drugs—Mifeprex, Tracleer, and Xyrem. In the case of Mifeprex, in 2002 FDA conducted routine inspections of two of the drug's distributors to oversee their compliance with distribution restrictions. FDA inspectors reviewed standard operating procedures and other information in order to oversee adherence to the requirements of the restricted distribution program such as procedures for maintaining signed provider agreements, distributing medication guides with shipments of the drug, and maintaining the physical security of the drug. For one of the inspections of Mifeprex distributors, FDA did not issue a citation. For the other inspection, FDA issued a citation in which the agency cited four

[54]FDA approved six of the nine Subpart H restricted drugs with a requirement that the sponsor report periodically to FDA specifically on implementation of the respective restricted distribution program. Under FDAAA, sponsors of all drugs with an approved REMS will be required to submit periodically to FDA an assessment of their REMS. Pub. L. No. 110-85, § 901(b), 823 Stat. 929, 932, *codified at* 21 U.S.C. § 355-1.

[55]Though FDA's Subpart H regulations provide an expedited process for withdrawing marketing approval for a drug if FDA determines that promotional materials are false or misleading, the agency has not done so for a Subpart H drug. See 21 C.F.R. § 314.530(a)(5) (2007). However, it has issued warning letters citing the sponsors for two of the drugs—Thalomid and Tracleer—for promoting unapproved use of the drug in violation of FDA regulations.

inconsistencies between the approved distribution plan and the distributor's standard operating procedures. For example, FDA cited the distributor for the absence of certain written procedures pertaining to the distribution of the drug. The sponsor responded to this citation, noting that at the time of approval the distribution plan did not require that distributors prepare such written procedures. Other examples of the inconsistencies FDA noted were serial numbers that had not been properly recorded on a shipping label as required for tracking purposes and the requirement that a medication guide be provided with each dose of the drug was not reflected in the written procedures for processing orders. As a result of its 2006 inspection of the Tracleer restricted distribution program, FDA did not issue a formal citation, but provided recommendations to the sponsor. In its 2007 inspection of the Xyrem restricted distribution program, FDA did not identify any specific deficiencies.[56] However, many of the responsibilities for the program are contracted out to a pharmacy, which was not inspected. The inspection report notes that, for that reason, FDA could not verify whether the sponsor had fulfilled the requirements for the drug's restricted distribution program.

Although FDA's inspections for Mifeprex and Tracleer led to recommendations for improving the respective restricted distribution programs, through the end of 2007, FDA had not conducted inspections of compliance with restricted distribution requirements for six Subpart H restricted drugs. FDA officials told us that the agency has conducted

[56]FDA's inspection report notes that the sponsor refused to provide FDA access to full reports from audits that the sponsor had conducted to evaluate its contractors' compliance with agreed upon responsibilities under the restricted distribution program.

inspections of compliance with distribution restrictions for three additional drugs since the beginning of 2008.[57, 58]

To Oversee Compliance with Postmarketing Study Commitments, FDA Relied on Sponsors' Data That Found That Most Have Unfulfilled Commitments

For the eight Subpart H restricted drugs approved with postmarketing study commitments, FDA has relied on sponsors' annual reports for updates on the status of each commitment. FDA's reviews of these reports are the basis for its determination of the status of each commitment as fulfilled, submitted, pending, ongoing, delayed, released, or terminated. FDA officials told us that the status of postmarketing study commitments for Subpart H drugs is monitored the same way as those commitments for other drugs.

Seven of the eight Subpart H restricted drugs approved with postmarketing study commitments had at least one commitment that was not fulfilled as of September 2007.[59] Of these seven drugs, most have study commitments that FDA has classified as ongoing, pending, or delayed.[60] In the case of Mifeprex, FDA had categorized both of the drug's postmarketing study commitments—to which the sponsor agreed at time of the drug's approval in 2000—as ongoing until December 2007 when the agency changed the status of one of the commitments to released. For the first commitment—a study to compare outcomes for patients whose

[57]In 2008, FDA conducted initial inspections specific to the restricted distribution programs for Accutane, Actiq, and Revlimid. In addition, FDA conducted a second such inspection for the Tracleer program. As of May 13, 2008, the results from these inspections were not available.

[58]In February 2007, agency officials told us that they were working to establish a process to conduct regular inspections to oversee sponsors' compliance with distribution restrictions for Subpart H restricted drugs. Since that time, agency officials told us that FDA had decided to combine the inspection of restricted distribution programs with inspections examining compliance with adverse event reporting requirements. However, agency officials noted in May 2008 that FDA is reevaluating its process for conducting inspections in light of recent legislative changes. Under FDAAA, FDA is required to evaluate, at least annually, for one or more drugs that have elements to assure safe use as part of their REMS, whether those elements assure the safe use of the drug, are not unduly burdensome on patient access, and to the extent practicable minimize the burden on the health care delivery system. 21 U.S.C. § 355-1(f)(5)(B).

[59]FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarket study commitments and has submitted the final report for the third and final commitment.

[60]In its June 2006 report on FDA's management of postmarket studies, the Department of Health and Human Services Office of the Inspector General found that it is common across all drugs approved by FDA with postmarket study commitments for sponsors to have unfulfilled commitments.

health care providers perform a surgical abortion with outcomes for patients who are referred to another facility for follow-up care in the event of treatment failure—the sponsor has reported difficulty in enrolling participants into the study. FDA told us that according to the sponsor, the "vast majority of prescribers" can provide surgical abortion services on site. FDA has opted not to terminate the study, and has categorized it as ongoing. FDA officials told us that this gives the agency additional flexibility in the event that provider or practice patterns change over time, making enrollment of study participants more feasible. The sponsor also has reported enrollment challenges in the case of the second study commitment for Mifeprex—to conduct surveillance of ongoing pregnancies following failure of treatment. FDA officials told us that postmarket experience with the drug has shown that most patients opt to have a surgical abortion in the event that the Mifeprex regimen is not successful in terminating the pregnancy. In December 2007, FDA released the sponsor from this commitment because it determined that the study will no longer provide helpful information because of low enrollment.

FDA has worked with some of the sponsors of the Subpart H restricted drugs to make adjustments to agreed upon commitments that have not been completed.[61] FDA officials told us that the agency has in some cases made changes to a sponsor's postmarketing study commitments or requested new commitments in addition to those specified at approval. For example, FDA recommended several additional postmarketing study commitments for Thalomid following the agency's approval of an expanded indication for the drug. In the case of Tracleer, FDA recommended changes to some of the drug's study commitments. FDA had not requested additions or changes to the postmarketing study commitments for Mifeprex until the agency released the sponsor from its commitment to conduct surveillance of ongoing pregnancies following failure of treatment.

[61]FDA may withdraw approval of a drug approved under Subpart H if a sponsor does not carry out its required postmarketing studies with due diligence. 21 C.F.R. § 314.530(a)(2) (2007). According to FDA, the regulations only require postmarketing study commitments for drugs approved under the surrogate endpoint provision (21 C.F.R. § 314.510) and not for drugs approved under the restricted distribution provision (21 C.F.R. § 314.520). FDAAA provides FDA with additional authority with regard to requiring postmarketing studies and/or trials. See 21 U.S.C. § 355(o)(3).

To Oversee Compliance with Adverse Event Reporting Requirements, FDA Reviewed Sponsors' Data, Conducted Inspections and Identified Deficiencies for Most of the Drugs

To oversee compliance with adverse event reporting requirements, FDA has both reviewed data submitted by sponsors in required reports and conducted inspections. Sponsor reporting for the drugs has included annual reports in which the sponsor provided a summary of the adverse events reported in the previous year; periodic update reports which inform FDA of adverse events monthly, quarterly, or at some other interval established by FDA; and 15-day alert reports for events that are both serious and unexpected. In addition, in some cases sponsors have agreed or FDA has required them to provide 15-day alert reports for other types of serious adverse events. For example, the sponsor of Mifeprex agreed to provide 15-day alert reports for cases of serious infection and ruptured ectopic pregnancy in women who used the drug, and FDA required the sponsor of Thalomid to report suspected or confirmed pregnancy in women taking that drug.[62] In some cases, including for Mifeprex, FDA specifically documented its assessments of adverse event reporting contained in annual, periodic update, or 15-day alert reports or reports submitted to the AERS database. FDA officials told us that staff review all submitted reports, but do not always document their reviews.

In addition to relying on reports submitted by the sponsors, FDA has conducted inspections specifically to oversee the sponsors' compliance with adverse event reporting requirements for eight of the nine drugs, including Mifeprex.[63] Between 2001 and May 2008, FDA had conducted 19 such inspections with a range of none to four inspections conducted for each drug.[64] In the case of Mifeprex, FDA has conducted three inspections—in 2002, 2004, and 2006—related to adverse event reporting. In these inspections, FDA reviewed a variety of documents pertaining to adverse event reporting for Mifeprex, including standard operating procedures, product labeling, MedWatch reporting forms, 15-day alert

[62]Mifeprex labeling specifically cautions against the use of the drug in women with ectopic pregnancy. The sponsor has noted that the condition is not an adverse drug experience as FDA defines the term.

[63]As of May 2008 FDA had not conducted an adverse event reporting inspection for the sponsor of Revlimid since this drug was approved under Subpart H. The agency inspected Celgene—the sponsor of Revlimid and Thalomid—in 2001, 2002, 2004, and 2005, but these inspections occurred before Revlimid was approved in December 2005. FDA officials told us they did not have specific goals for how frequently sponsors are inspected to monitor compliance with adverse event reporting requirements.

[64]These inspections include two inspections of the sponsor of Accutane (isotretinoin). FDA conducted an additional four adverse event reporting inspections of sponsors or the manufacturer of generic isotretinoin products.

reports, complaint file, periodic update reports on adverse events, and annual NDA reports. In addition, FDA documented reviews of samples of the sponsor's adverse event reports for completeness, accuracy, and timeliness.

As a result of the Mifeprex inspections, FDA issued citations for deficiencies related to the accuracy, completeness, or timeliness of some reports as well as for the sponsor's failure to follow certain procedures for handling some adverse event follow-up activities. In each of the Mifeprex inspections, FDA identified some examples of misclassified reports—events which FDA said should have been submitted as 15-day alert reports rather than in periodic reports. For example, FDA cited the sponsor for not classifying some events resulting in hospitalization as serious events and thus not reporting those events as 15-day alert reports. In another inspection, FDA found that some of the sponsor's procedures for reporting and following up on adverse events were inadequate or had not been developed. These deficiencies were similar to those FDA found for other drugs, and FDA identified fewer problematic reports for Mifeprex than for some of the other Subpart H restricted drugs. Following each of the inspections for Mifeprex, the sponsor provided a written response to FDA in which it either agreed to address FDA's findings or noted its disagreement with the deficiencies FDA cited. For example, following the first inspection, the sponsor agreed to address the examples of misclassified or incomplete reporting FDA cited and to reinforce procedures for handling adverse event-related correspondence with its staff. In some cases the sponsor disagreed with FDA's characterization of a deficiency or presented evidence to refute a claim that it had not complied with a reporting requirement or procedure.

As a result of FDA's inspections for the other seven drugs, the agency issued written citations to six of the sponsors for deficiencies. In addition, FDA noted only "oral observations" for the other sponsor. Similar to the Mifeprex inspections, FDA staff reviewed information such as sponsor documentation and standard operating procedures related to adverse event reporting for the other seven drugs for which it conducted inspections. As it did for the Mifeprex inspections, FDA reviewed samples of adverse event reports for completeness, accuracy, or timeliness for most of the other drugs. As it did with Mifeprex, FDA cited some sponsors for deficiencies such as incomplete or late reporting of adverse events or failure to adhere to certain procedures for reporting. For example, FDA cited the sponsor of Thalomid for failure to submit several reports of serious and unexpected adverse events as a 15-day alert report and for late reporting of some other adverse events that included deaths and

hospitalizations. In addition, FDA issued an untitled letter to the sponsor citing its failure to review and submit 82 reports of serious and unexpected adverse events within the required time frame.

FDA was not always consistent in how it documented deficiencies in adverse event reporting. In some of its inspections FDA documented the same type of deficiency as a citation while in others it noted them as oral observations or discussion points. For example, FDA did not issue a citation for the sponsor of Tracleer after inspectors noted 52 late 15-day reports—instead discussing the late reports with the sponsor at the close of the inspection. However, in its first inspection of the sponsor for Mifeprex, FDA issued a citation for failure to file a single 15-day report within the required 15 days. FDA also cited the sponsor for 6 late 15-day reports in each of its two subsequent inspections, although the sponsor refuted this finding in written responses following each inspection. As in the case of Mifeprex, sponsors responded to FDA in writing to describe actions they had taken to address deficiencies or to disagree with FDA's conclusions following an inspection.

To Oversee Postmarket Safety, FDA Used Similar Methods to Review Reported Adverse Events and Took a Variety of Actions in Response to Emerging Concerns

FDA has used similar methods to oversee postmarket safety—monitoring, investigating, and taking action on emerging safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. For Mifeprex, FDA has routinely reviewed the available information on reported adverse events from sources such as annual reports, periodic update reports, 15-day alerts, and data from its AERS database. Since the time Mifeprex was approved, FDA has documented regular reviews and summarized the available data on adverse event reports to monitor the drug's safety. FDA believes that, because the distribution system for Mifeprex requires that prescribing physicians agree to report hospitalizations and other serious adverse events, it is unlikely there are significant numbers of these events that are not reported to FDA. However, FDA acknowledges that because the reporting system is voluntary, the agency cannot be certain that they have reports of all serious adverse events.

FDA officials have concluded that, with the exception of the cases of fatal infection, the reported serious adverse events associated with Mifeprex have been within or below the ranges expected based upon the medical literature on adverse events following medical abortion. In its May 2006

response to congressional inquiries regarding Mifeprex,[65] FDA stated that the most commonly reported serious adverse events had been blood loss requiring a transfusion, infection, and ectopic pregnancy. FDA estimated that 0.023 percent of U.S. women who had taken Mifeprex have required transfusion, compared to a transfusion rate of 0.15 percent observed in international studies of the drug. FDA also noted that the rate of ectopic pregnancy among U.S. women who had used Mifeprex was 0.005 percent, compared to the overall rate of 1.3 to 2 percent in all U.S. pregnancies. Based on the medical literature, FDA estimated that fewer than 1 percent of patients will develop an infection of any kind following medical abortion with Mifeprex.

According to FDA, as of May 2008, among the estimated 915,000 U.S. women who had taken Mifeprex for termination of pregnancy since its approval, the agency was aware of seven deaths that may be related to the use of the drug.[66] Six of the deaths were due to severe infection, and one death involved an undiagnosed ectopic pregnancy. Of the cases involving infection, five of the women were infected with a rare bacterium, *Clostridium sordellii*, while one woman was infected with the bacterium *Clostridium perfringens*. With assistance from the Centers for Disease Control and Prevention (CDC) and other outside experts, FDA has investigated all reported infection-related deaths in U.S. women who have taken the Mifeprex regimen for termination of pregnancy. These investigations included requesting the medical records and autopsy reports for each case; evaluating available adverse event data from the United States, the United Kingdom, and the World Health Organization; consulting with scientific experts and health care providers from inside and outside FDA; and microbiological testing to identify the bacterium involved. In addition, FDA evaluated samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths to test for contamination with the bacteria.[67] FDA found that in the six cases of death

[65]FDA statement to the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, May 17, 2006.

[66]In her testimony to Congress on May 17, 2006, Dr. Janet Woodcock stated FDA was aware of five infection-related deaths in U.S. women. In the course of GAO's research for this study, FDA reported that an additional infection-related death occurred in 2007. In her testimony, Dr. Woodcock also discussed three other cases of deaths in U.S. women who had taken Mifeprex that, following investigation, were determined unlikely to be related to the use of the drug. In addition, she discussed three women in other countries whose deaths were related to the use of mifepristone and misoprostol for medical abortion.

[67]The product tracking provision of the restricted distribution program for Mifeprex enabled FDA to locate the lot numbers for the drugs administered in each of the cases.

due to infection, the women used a regimen of Mifeprex and misoprostol that has not been approved by FDA.[68] FDA has stated that it is aware that many health care providers use modified regimens, and while some of the regimens have been described in the medical literature, FDA has not evaluated the safety and effectiveness of any other regimen than the one described in the drug's approved labeling.

To further explore the nature of the infections, FDA initiated an interagency scientific workshop in May 2006 with CDC and the National Institutes of Health entitled "Emerging Clostridial Disease." These agencies had observed a general increase in the United States in reports of serious clostridial infections including infections in women who had used Mifeprex, that raised questions about *Clostridium's* relationship to fatal illness and pregnancy. According to the meeting minutes, participants discussed recent cases of clostridial infection—including those occurring among women who had taken Mifeprex and misoprostol for termination of pregnancy and those who had not—reviewed what was currently known about these infections, and discussed how to conduct surveillance to ensure that cases and trends of clostridial infections are monitored. At the workshop, a CDC official reported on the history of clostridial infections, including a cluster of ten fatal cases reported in the literature between 1977 and 2001 among previously healthy women. Of the ten cases, eight of the women became infected following childbirth, one became infected following a medical abortion, and the other case was unrelated to pregnancy.

As a result of its investigative efforts, FDA has concluded that the evidence does not indicate that Mifeprex caused the fatal infections. In response to congressional inquiry, FDA stated that "the nature of the relationship between taking a single dose of the drug and the reported cases of serious infection with a rare bacterium is highly uncertain."[69] Laboratory testing of samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths due to infection has

[68]In the case of five of the deaths in the U.S. due to infection, the women used an oral dose of Mifeprex, followed by a dose of misoprostol taken intravaginally. In the other case of death due to infection, the woman used an oral dose of Mifeprex followed by a dose of misoprostol taken by inserting it in the pouch of the cheek. The regimen approved by FDA calls for swallowing doses of both Mifeprex and misoprostol.

[69]See FDA letter to Representative Mark E. Souder, then-Chairman of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, U.S. House of Representatives, July 31, 2006.

shown no evidence of contamination with the bacteria.[70] FDA officials have said that the relationship between the infections and the use of unapproved regimens of Mifeprex and misoprostol remains unknown. Some research has suggested that the use of Mifeprex may suppress the immune system which could lead to infection. However, FDA has noted that if this were the case, the agency would expect to see a higher rate of other types of serious infections in patients who had used the drug, which has not been the case. FDA has noted that findings by the CDC and in the medical literature suggest that pregnancy itself—rather than the medication—may be the critical risk factor for women who have become infected with *Clostridium sordellii*.

FDA, working with the drug's sponsor, has taken a variety of steps—such as issuing warnings and making changes to the product labeling—to address safety concerns for Mifeprex that were identified through postmarket monitoring and investigation. For example, in response to reports of ruptured ectopic pregnancy, FDA developed a questions and answers document about the condition and worked with the drug's sponsor to alert health care providers and to highlight the importance of careful screening for the condition. In addition, FDA approved a labeling change to provide information about the importance of evaluating patients for ectopic pregnancy. In response to concerns about serious infections and associated deaths—all of which involved an off-label use of the drug—FDA issued Public Health Advisories to notify healthcare providers about patient deaths and the treatment regimens used in those cases, and to remind them of the regimen FDA has approved, and that FDA has not established the safety of alternative regimens. In addition, FDA issued a news release, reviewed letters from the sponsor to health care providers and emergency room directors to alert them to the safety concerns regarding serious infection, and approved changes to product labeling including revisions to the warning to include information about the deaths due to serious infection.[71] FDA also has established a Web site with information about Mifeprex, questions and answers about the drug, and

[70]FDA officials told us that the agency did not test for bacterial contamination of the specific lot associated with the most recent death because examination of the prior lots revealed no contamination.

[71]FDA officials told us that the sponsor distributed a letter to all health care providers who had signed the prescriber's agreement as of the time of the distribution of the letter and distributed a letter to all emergency room directors in the United States.

links to other safety-related information.[72] FDA used labeling changes—including updating the medication guide that prescribers agree to discuss with their patients—and information posted on its Web site to remind consumers and health care providers that FDA has not assessed the safety and efficacy of any regimen other than the one approved for the drug and indicated in its labeling.

FDA has similarly monitored adverse events for the other Subpart H restricted drugs. As FDA has done with Mifeprex, the agency has documented periodic safety reviews of the available information it had on reported adverse events for all of the other drugs. FDA's reviews analyzed data on reported adverse events from sources such as annual NDA reporting, periodic update reports, 15-day alerts, and data from the AERS database. Some FDA reviews summarized the available data on a specific type of adverse event—like liver toxicity, or severe bleeding—or adverse events in general, in order to determine whether the data suggest an emerging safety concern for the drug. In addition, in some cases, as it did with Mifeprex, FDA has sought the advice and assistance of other federal agencies and outside experts to investigate serious adverse events.

As a result of its monitoring activities, FDA has identified postmarket safety concerns for most of the Subpart H restricted drugs and has taken similar actions to address them. When FDA has found safety concerns related to a Subpart H restricted drug, it has worked with the drug's sponsor to employ a variety of measures to ensure the drug's safe use. These have included adding or strengthening a warning on the label, issuing a Public Health Advisory, and sending letters to health care providers to alert them to a safety risk. FDA has approved safety-related labeling changes, such as boxed warnings, for eight of the nine drugs. In the case of four of the drugs, including Mifeprex, the agency issued a Public Health Advisory or Safety Alert. The sponsors of five of the drugs including Mifeprex sent a letter to health care providers who prescribe (or may prescribe) the drug to alert them of safety concerns or to communicate new information regarding the drug. For example, in the case of Tracleer, adverse event reports revealed an increased risk of liver damage in patients who were treated with the drug. As a result, FDA and the sponsor notified health care providers of the risk by issuing a Safety Alert, highlighting the need for continued monitoring of liver function in

[72]FDA's Web site for Mifeprex safety information is located at: http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm

patients using the drug. The sponsor added a boxed warning about potential liver injury to the labeling and issued a letter to health care providers to alert them to the potential risk. In general, the actions FDA took in response to safety concerns were similar across all of the drugs.

Agency Comments

We provided HHS with a draft of this report for review. HHS informed us that it did not have general comments on the draft report. In addition, HHS provided technical comments, which we incorporated as appropriate.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to others who are interested and make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staffs 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 may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.

Marcia Crosse
Director, Health Care

Appendix I: Select Drugs Approved by FDA with Restricted Distribution

Drugs approved under the restricted distribution provision of Subpart H	Condition treated	Application type (year first approved under Subpart H)
Accutane (isotretinoin)	Severe recalcitrant nodular acne.	Supplemental NDA (2005)
Actiq (oral transmucosal fentanyl citrate)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy.	NDA (1998)
Lotronex (alosetron hydrochloride)	Severe diarrhea predominant irritable bowel syndrome (IBS) in women who have: chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and failed to respond to conventional therapy.	Supplemental NDA (2002)
Mifeprex (mifepristone)	Medical termination of intrauterine pregnancy through 49 days' pregnancy.	NDA (2000)
Plenaxis (abarelix for injectable suspension)	Palliative treatment of men with advanced symptomatic prostate cancer, with specified risks or symptoms.	NDA (2003)
Revlimid (lenalidomide)	Treatment of a limited subset of patients with transfusion dependent anemia.	NDA (2005)
	Treatment of multiple myeloma patients who have received at least one prior therapy.	Supplemental NDA
Thalomid (thalidomide)	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.	NDA (1998)
	Newly diagnosed multiple myeloma.	Two Supplemental NDAs[a]
Tracleer (bosentan)	Pulmonary arterial hypertension.	NDA (2001)
Xyrem (sodium oxybate)	Cataplexy associated with narcolepsy.	NDA (2002)
Select Drugs with restricted distribution imposed outside of Subpart H		**Application type (year first approved)**
Clozaril (clozapine)	Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.	NDA (1989)
Tikosyn (dofetilide)	Irregular heartbeats (atrial fibrillation and atrial flutter).	NDA (1999)
Trovan (trovafloxacin/ alatrofloxacin)	Serious, life- or limb-threatening infections in an inpatient healthcare setting.	n/a[b] (1997)

Source: GAO analysis of FDA data.

Note: We list each drug by its trade name with its chemical name in parentheses.

[a]These supplemental NDAs were approved under both the restricted distribution and surrogate endpoint provisions of Subpart H.

[b]Trovan was not originally approved with distribution restrictions. Based on postmarket evidence of serious liver injury in some patients, the sponsor agreed to FDA's requests to limit the distribution of Trovan to patients with specific symptoms only in inpatient settings. However, these restrictions were not associated with a supplemental application.

Appendix II: Detailed Description of Distribution Restrictions for Mifeprex

FDA approved Mifeprex with the following specific restrictions on distribution:

- Mifeprex must be provided by or under the supervision of a physician who possesses adequate qualifications and agrees to provide the treatment according to several guidelines. To accomplish this, the system required that prescribing physicians register with an authorized distributor by providing a signed Prescriber's Agreement attesting to the following:
  - Possesses the ability to assess the duration of pregnancy accurately.
  - Possesses the ability to diagnose ectopic pregnancies.
  - Possesses the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
  - Has read and understood the prescribing information about Mifeprex.
  - Will provide each patient with a medication guide and fully explain the procedure to each patient, provide her with a copy of the medication guide and Patient Agreement, give her an opportunity to read and discuss both the medication guide and the Patient Agreement, obtain her signature on the Patient Agreement and sign it as well.
  - Will notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
  - Will report any hospitalization, transfusion or other serious events to the sponsor or its designate.
  - Will record the Mifeprex package serial number in each patient's record.
- Provisions for the physical security of the drug during distribution such as
  - Direct distribution of the drug through select authorized distributors to physicians who have signed the Prescriber's Agreement, which includes providing their medical license number. Distributors are

required to ensure that the physician is registered before distributing the drug.

- Secure manufacturing, receiving, distribution, shipping, and return procedures, including unique serial numbers on packaging and tamper-proof seals.

Appendix III: Prescriber's Agreement for Mifeprex Distribution

The following is the prescriber's agreement at the time of the Mifeprex approval. Under the restricted distribution program for Mifeprex, the agreement is provided—by the sponsor's licensee Danco Laboratories, Inc.—to all providers to be signed and returned before the prescriber can receive any shipments of Mifeprex.

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex® (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

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

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Jill Center; Chad Davenport; and Cathy Hamann made key contributions to this report. Julian Klazkin also contributed.

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Appendix 4

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of its members, ET AL.,	)	
Plaintiffs,	)	Case No. CV-2011-1722
v.	)	
TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health, ET AL.,	)	Judge Daniel L. Owens
Defendants.	)	

DECLARATION OF DANIEL A. GROSSMAN, M.D. IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

DANIEL A. GROSSMAN, M.D., hereby declares, under penalty of perjury, that the following statements are true and correct:

1. I provide the following facts and opinions as an expert in obstetrics and gynecology and the provision of medication abortion. I am Board-certified in obstetrics and gynecology and serve as a Senior Associate with Ibis Reproductive Health, a nonprofit organization that conducts clinical and social science research concerning sexual and reproductive health. I am also an Assistant Clinical Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco. In addition, I am a Fellow of the American College of Obstetricians and Gynecologists ("ACOG"), the nation's leading association of medical professionals specializing in obstetrics and gynecology. A copy of my curriculum vitae, which summarizes my background, experience, and publications, is attached hereto as Exhibit A.

2. The opinions expressed below are based on my years of experience in the field of obstetrics and gynecology; my research, writing, teaching, and clinical experience concerning medication abortion; and my review of the medical literature.

3. I have reviewed Oklahoma House Bill 1970. I believe it will prevent physicians from being able to provide patients with high level medical care according to their needs and expectations.

Off-Label Use of FDA-Approved Prescription Drugs

4. My understanding of the federal drug regulation process is that it is a commercial process. The United States Food and Drug Administration ("FDA") does not test protocols for drugs. Rather, a drug company performs or obtains data from one or more clinical trials. A drug company requests approval from the FDA to market a drug for use for particular indications at a certain dosage, and submits a label for approval.

5. The term "off-label use" refers to the use of a prescription drug for indications and/or in dosages other than those expressly approved by the FDA and set forth in the drug's Final Printed Label ("FPL").

6. Off-label use of FDA-approved medications allows physicians to implement advances in medicine with respect to a medication, despite the fact that there may not be a commercial reason for the manufacturer to market that medication for all of the uses supported by scientific evidence. FDA-approved labeling is often out of date or not based on current scientific evidence. Even the FDA recognizes that advances in medicine often precede changes to labeling, an acknowledgement that an off-label use may constitute better health care.

Physicians prescribing a drug or device off- label are assumed to be well informed and to base their decision to do so on sound medical evidence.[1]

7. As a consequence of the dearth of clinical trials including pregnant women and children, off-label use is extremely common among pediatricians and obstetricians. In one study, physicians prescribed medications for an off-label indication to 23% of women attending prenatal clinics.[2] And as much as 50% of pediatric use of medications is considered off-label.[3]

8. Many prescription drugs have common off-label uses. For example, oral contraceptives are commonly prescribed off-label to reduce menstrual bleeding and cramping, or to prevent ovarian cysts.

9. Off-label use of medications is an integral part of providing healthcare in the United States. In my opinion, there is no medical reason to restrict off-label use of a drug that is founded on high-quality evidence simply because it is used for termination of pregnancy.

Off-Label Use of Methotrexate to Treat Women With Ectopic Pregnancies

10. Approximately two percent of all pregnancies are ectopic pregnancies. An ectopic pregnancy occurs when a fertilized egg implants outside a woman's uterus. Roughly 97% of ectopic pregnancies are located in the woman's fallopian tube. An ectopic pregnancy is always a risk to a woman's health and can be life-threatening.[4]

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[1] Grossman D, Ellertson C, Abuabara K, Blanchard K. Barriers to contraceptive use present in product labeling and practice guidelines. *Am J Pub Health* 2006; 96(5):791-799; Nightingale SL. Off-label drug use of prescription drugs. *Am Fam Physician.* 2003; 68:425-427.

[2] Rayburn WF, Turnbull GL. Off-label drug prescribing on a state university obstetric service. *J Reprod Med.* 1995; 40:186-188.

[3] Marcio A. da Fonseca &, Paul Casamassimo. *Old drugs, new uses.* 33 Pediatr Dent 67 (2011).

[4] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 94: Medical management of ectopic pregnancy. Obstet Gynecol. 2008 Jun;111(6):1479-85.

11. Surgical management of a woman's ectopic pregnancy carries risks to her health and her future fertility. Surgery for a tubal ectopic pregnancy can involve incising her fallopian tube to remove the pregnancy and then repairing it, or removing the fallopian tube in its entirety or in part.

12. Because of the risks associated with surgical management of ectopic pregnancy, off-label use of methotrexate, a cancer-treating drug, is often the preferred method of treatment. In a Practice Bulletin, ACOG has recommended this treatment option for certain women with ectopic pregnancies.[5] Use of methotrexate for treatment of ectopic pregnancy was an advance in healthcare for women; it avoids the risk of surgery and may reduce the risk of future infertility.

13. For appropriate candidates with ectopic pregnancy, off-label use of methotrexate is considered standard management.

Medication Abortion

14. Medication abortion entails the use of medications, rather than a surgical procedure, to terminate a pregnancy. For some women, medication abortion offers advantages over surgical abortion. Medication abortion can be performed earlier in pregnancy than surgical abortion and is less invasive. It is often medically advantageous for women with certain conditions, such as cervical stenosis (tightly closed uterus), uterine anomalies (i.e. bicornuate or double uterus), marked obesity, obstructive uterine fibroids, or malformations of the genital tract, to have a medication rather than a surgical abortion. Some women also consider it to be more private.

15. In the United States, medication abortions are most commonly induced using a combination of the medications mifepristone and misoprostol. Multiple regimens have been developed for medication abortion using these medications.

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[5] *Id.*

16. Medication abortions may also be induced using a combination of the drugs methotrexate and misoprostol.

17. Mifepristone blocks the hormone progesterone, which is needed to maintain a pregnancy. In the United States, it is manufactured and sold by Danco Laboratories, LLC, under the brand name Mifeprex. Mifeprex comes in 200 milligram ("mg") tablets. It must be taken orally.

18. Mifeprex is contraindicated for women with ectopic pregnancy not because it is dangerous for women with that condition but because it doesn't work to terminate a pregnancy outside the uterus.

19. Misoprostol is a prostaglandin analogue; it causes the cervix to open and the uterus to contract and expel its contents. Misoprostol comes in 100 microgram ("μg") and 200 μg tablets. It may be taken orally, buccally, sublingually or vaginally. Oral administration requires the patient to put the tablets of misoprostol in her mouth and swallow them. Buccal administration requires the patient to put the tablets of misoprostol between her gums and cheek and allow them to dissolve. Sublingual administration requires the patient to put the tablets under her tongue and allow them to dissolve. Vaginal administration requires the patient to insert the tablets of misoprostol into her vagina.

20. Misoprostol is not labeled for use in medication abortions. Accordingly, any use of misoprostol for a medication abortion, including the use described in the FPL for mifepristone, is "off-label."

21. Subsequent to the FDA's approval of mifepristone in 2000, other mifepristone/misoprostol regimens have been developed in an effort to reduce side effects and to make medication abortion safer, more effective, and less expensive. These regimens are generally referred to as "evidence-based regimens" in the medical literature. Because the

evidence-based regimens for medication abortion using mifepristone/misoprostol differ from the regimen described in the Mifeprex FPL, they constitute off-label use of the drug.

22. The use of evidence-based regimens for medication abortion allows women to receive, and physicians to provide, medical care that is tailored to their needs and preferences.

23. Evidence-based regimens for medication abortion are advantageous for women's health as compared to the regimen described in the Mifeprex FPL. Scientific studies have demonstrated that use of evidence-based regimens can make medication abortions safer and more effective than use of the FPL regimen.

24. In October 2005, ACOG issued a Practice Bulletin entitled *Medical Management of Abortion*, which included the following recommendation: "Compared with the FDA-approved regimen, mifepristone-misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP." ACOG accorded that recommendation a Level A rating, which is the highest possible rating based on high quality scientific studies. [6] A copy of the Practice Bulletin is annexed hereto as Exhibit B.

25. The World Health Organization and the Cochrane Collaboration have also concluded that the evidence-based regimens described in the ACOG bulletin are superior to other regimens for medication abortion.[7] The World Health Organization is a specialized agency of the United Nations that acts as a coordinating authority on international public health. Its objective is the

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[6] *See* American College of Obstetricians and Gynecologists, ACOG Practice Bulletin No. 67: Medical Management of Abortion, 106 Obstet. Gynecol. 871 (2005).

[7] World Health Organization, Safe Abortion: Technical and Policy Guidance for Health Systems (2003), *available at* http://www.who.int/reproductive-health/publications/safe_abortion/safe_abortion.pdf; Regina Kulier, *et al.*, Medical methods for first trimester abortion (Review), *Cochrane Database of Systematic Reviews* 2004, Issue 1, Art. No.: CD002855, DOI: 10.1002/14651858.CD002855.pub3.

attainment by all peoples of the highest possible level of health. The Cochrane Collaboration is an international nonprofit organization that is dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions.

26. Restricting the provision of medication abortion to the regimen described in the Mifeprex FPL would create barriers to access for women seeking this form of medical care. First, because the FPL regimen is only available to women whose pregnancies are less than or equal to 49 days, lmp, women whose pregnancies exceed 49 days lmp would be unable to obtain a medication abortion. However, evidence-based regimens have been proved safe and effective for women with pregnancies up to 63 days lmp.

27. Second, the FPL regimen uses three times as much mifepristone as, for example, the safer and more effective evidence-based regimen recommended by ACOG. It is therefore three times as expensive.

28. Third, the FPL regimen requires patients to return to the doctor's office for the administration of misoprostol. But evidence shows that women can safely administer misoprostol by themselves, at home.[8] Requiring a patient to return to her physician's office for the administration of misoprostol is medically unnecessary. It also increases the cost and inconvenience of the medication abortion procedure, as women must make additional arrangements for logistics like time off from work, child care, and travel. Cost can be a particularly significant barrier to access for low-income women. In addition, some women need

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[8] Wesley H. Clark, *et al.*, Can mifepristone medical abortion be simplified?: A review of the evidence and questions for future research, 75 Contraception 245 (2007).

to maintain the confidentiality of their abortion procedure, and requiring a return trip for the administration of misoprostol could make that more difficult.

29. Approximately 50% of women expel the products of conception within four hours of administration of misoprostol, and some might start doing so within an hour of administration.[9] Accordingly, requiring a woman to take misoprostol at a doctor's office increases the risk that she will expel the products of conception away from her home, possibly while driving, particularly if she lives far away from the doctor's office. In addition to the medical risks involved, expelling products of conception away from home and in a car is unnecessarily very unpleasant for women.

30. Studies have also shown that misoprostol is more effective in terminating pregnancy when taken buccally or vaginally than when taken orally as set forth in the mifepristone FPL.[10]

31. As a result of the scientific studies and the medical and practical considerations regarding administration of misoprostol, a large majority of the medication abortions in the United States currently involve a buccal or vaginal administration of misoprostol by the patient at home. One study showed that by 2001—only a year after mifepristone was approved by the FDA for termination of pregnancy—96% of facilities where abortions were performed allowed their clients to self-administer misoprostol at home.[11]

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[9] Irving M. Spitz, et al., *Early pregnancy termination with mifepristone and misoprostol in the United States.* 338 New Eng. J. Med. 1241 (1998).

[10] Beverly Winikoff et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Controlled Trial*, 112 Obstet. & Gynecol. 1303, 1304-05, 1309 (2008); Eric A. Schaff, et al., *Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion*. 64 Contraception 81 (2001); Hazem El-Refaey, et al., *Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol.* 332 New Eng. J. Med. 983 (1995).

[11] Melanie M.J. Wiegerinck et al., *Medical abortion practices: a survey of National Abortion Federation members in the United States*, 78 Contraception 486, 488 (2008).

32. To effectively assess the risks related to mifepristone, it is important to put them in context. Women who seek medication abortions are pregnant, and pregnancy, itself, is risky. The risk of death following medication abortion is roughly 0.6 deaths/100,000 procedures. This risk is roughly comparable to the risk of death following a miscarriage. It is also comparable to the risk of death related to abortion overall, which is 0.7 deaths/100,000 procedures.

33. The risk of death from fatal anaphylactic shock following use of penicillin in the United States is 2.0 deaths/100,000 uses.[12]

34. From the time that Mifeprex was approved by the FDA in 2000 through September 2010, eight fatal infections with species of Clostridium bacteria following abortions using mifepristone and misoprostol have been reported in the United States. An additional fatal infection was also reported in Canada during a clinical trial. There is no evidence that these infections were caused by mifepristone or misoprostol.

35. Fatal infections with species of Clostridium bacteria have also been known to occur after different kinds of obstetric and gynecologic procedures, including live birth by vaginal delivery or cesarean section; cervical dysplasia; surgical abortion; and stillbirths.

36. Complications associated with medication abortion are not common. Complications include hemorrhage, infection, and ongoing pregnancy, while side effects include nausea and diarrhea, cramps, and fever. Hospitalization due to complications from medication abortion is rare.

37. Accordingly, a requirement that physicians follow the regimen set forth in the FPL for mifepristone is not supported by medical evidence. In addition, it subjects women to increased risks of side effects such as nausea, vomiting, cramping, and diarrhea; it increases the

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[12] Neugut, AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch. Intern. Med. 2001; 161:15-21.

cost of a medication abortion by a substantial amount, and it prevents women who are beyond 49 days LMP from obtaining a medication abortion. Not surprisingly, one study showed that even by one year after the FDA approved the use of mifepristone for termination of pregnancy, only four percent of facilities providing medication abortions were following the regimen set forth in the FPL, and those whose staff had attended accredited Continuing Medical Education sessions, where information on recent advances in the field and best practices are shared, were more likely to use evidence-based regimens as compared to clinics without similarly trained staff.[13]

38. Oklahoma House Bill 1970 will compromise the quality of care available to women. In clinical situations where medication abortion is the medically preferred method for terminating a woman's pregnancy, withholding that option means she is left with a method that is inferior from a medical perspective. Some women prefer medication abortion over surgical abortion; denying them that option means they are not getting optimal care.

Daniel A. Grossman MD

DANIEL A. GROSSMAN, M.D.

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[13] Melanie M.J. Wiegerinck et al., *Medical abortion practices: a survey of National Abortion Federation members in the United States*, 78 Contraception 486, 488, 89 (2008).

Exhibit A

September 20, 2011

DANIEL A. GROSSMAN, M. D., F. A. C. O. G.

Ibis Reproductive Health
1330 Broadway, Suite 1100
Oakland, CA 94612
Phone: 510-986-8941; Fax: 510-986-8960
Email: dgrossman@ibisreproductivehealth.org

Current position

Senior Associate, Ibis Reproductive Health, San Francisco

Education

Sept. 1985-May 1989	Yale University-Molecular Biophysics and Biochemistry	B.S., 1989
Sept. 1989-June 1994	Stanford University School of Medicine	M.D., 1994
June 1994-June 1998	Resident and Administrative Chief Resident, Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco	

Licenses/Certification

1996-Present	California medical licensure (A60282)
2001-Present	Board-certified, American Board of Obstetrics and Gynecology

Principal positions held

Aug. 1998-Feb. 2003	
Aug. 2005-Present	Physician, St. Luke's Women's Center, San Francisco, CA
May 2003-Aug. 2005	Health Specialist, The Population Council Regional Office for Latin America and the Caribbean, Mexico City
Aug. 2005-Present	Senior Associate, Ibis Reproductive Health

Other positions held concurrently

Aug. 1998-Feb. 2003	Director of Medical Student Education, Department of Obstetrics and Gynecology, St. Luke's Hospital
Aug. 1998-Feb. 2003	Vice Chair, Department of Obstetrics and Gynecology, St. Luke's Hospital
Aug. 1998-Present	Assistant Clinical Professor, Bixby Center for Global Reproductive Health, Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco

Honors and awards

1988	Howard W. Hilgendorf Jr. Fellowship, Yale University
1988	Robin Berlin Memorial Prize, Yale University
1989	Magna cum laude, Yale University
1990	Medical Scholars Award, Stanford University
1990	Peter Emge Traveling Fellowship, Stanford University
1991-1992	Foreign Language and Area Studies Fellowship, Stanford University
1994	Dean's Award for Research in Infectious Diseases, Stanford University

Honors and awards (continued)

2007 Ortho Outstanding Researcher Award, Association of Reproductive Health Professionals
2009 Visionary Partner Award, Pacific Institute for Women's Health
2010 Scientific Paper Award, National Abortion Federation

Key words/areas of interest

Abortion, medication abortion, second trimester abortion, contraception, over-the-counter access to oral contraception, integration of family planning into HIV care and treatment, Latina reproductive health in the US, misoprostol and self-induction of abortion, Mexico, Peru, Bolivia, Dominican Republic, South Africa, Kenya

PROFESSIONAL ACTIVITIES

Clinical activities

St. Luke's Women's Center: Since August 2005, I have worked as a consultant at St. Luke's Women's Center, where my clinical activities focused on general obstetric and gynecology care, including providing abortion up to 20 weeks' gestation, as well cervical dysplasia care (including office-based LEEP). In addition to providing outpatient services, I staffed Labor and Delivery and provided gynecologic coverage for the emergency room. Since August 2010, I have only been providing inpatient coverage for St. Luke's Women's Center.

PROFESSIONAL ORGANIZATIONS

Memberships

2000-Present: Fellow, American College of Obstetrics and Gynecology
2006-Present: Fellow, Society of Family Planning
2004-Present: American Public Health Association
2004-2011: Association of Reproductive Health Professionals
2004-Present: International Consortium for Medical Abortion
2006-Present: Liaison Member, Planned Parenthood Federation of America National Medical Committee
2005-Present: Consorcio Latinoamericano contra el Aborto Inseguro (Latin American Consortium against Unsafe Abortion)
2004-Present: Working Group on Oral Contraceptives Over-the-Counter

Service to professional organizations

2008-Present: Society of Family Planning, reviewer of fellow research protocols, reviewer of grant proposals, abstract reviewer for annual meeting
2007-Present: American Public Health Association, Governing Councilor (2007-2009, 2010-2012), Section Secretary (2008-2009), abstract reviewer for annual meeting
2005-Present: Consorcio Latinoamericano contra el Aborto Inseguro, member of Coordinating Committee
2006-Present: Working Group on Oral Contraceptives Over-the-Counter, working group coordinator and member of steering committee
2010-Present: Member, Committee on Practice Bulletins-Gynecology, ACOG
2010-Present: Steering Committee member, International Consortium for Medical Abortion

SERVICE TO PROFESSIONAL PUBLICATIONS

2004-Present Ad hoc reviewer for Obstetrics and Gynecology (5 papers in past 5 years), American Journal of Public Health (2 papers in past 3 years), Reproductive Health Matters (6 articles in past 4 years), Expert Review of Obstetrics and Gynecology (1 review in past year), and Women's Health Issues (4 articles in past 2 years)

INVITED PRESENTATIONS (Selected)

International

Reducing Maternal Mortality due to Abortion: Potential Impact of Misoprostol in Low-resource Settings. XVIII FIGO World Congress of Gynecology and Obstetrics, Kuala Lumpur, 2006 (oral presentation and session chair).

Mortality and morbidity following second trimester abortion. International Consortium for Medical Abortion Conference on Second Trimester Abortion, London, 2007 (invited talk).

Abortion research developments. Future of abortion: controversies and care, London, 2008 (invited talk).

Integration of family planning into HIV care in Western Kenya. What do providers think? XIX FIGO World Congress of Gynecology and Obstetrics, Cape Town, South Africa, 2009 (oral presentation)

Cost-effectiveness of alternative strategies for first-trimester abortion in Mexico City. XIX FIGO World Congress of Gynecology and Obstetrics, Cape Town, South Africa, 2009 (oral presentation and session chair)

National

How useful are routine follow-up visits after first trimester abortion? National Abortion Federation 27th Annual Meeting, New Orleans, 2004 (oral presentation).

Validation of a semi-quantitative urine pregnancy test: an alternative technology to rule-out ongoing pregnancy after medical abortion. National Abortion Federation Annual Meeting, Montreal, 2005 (oral presentation).

Women's experiences crossing from Mexico to San Diego to access safe, legal abortion services. American Public Health Association Annual Meeting, Philadelphia, 2005 (oral presentation).

Self-screening for contraindications to oral contraceptive use: evidence for the safety of over-the-counter provision. Annual meeting of the Association of Reproductive Health Professionals and the Society of Family Planning, Minneapolis, 2007 (oral presentation). Received the Ortho Outstanding Researcher Award for this presentation.

Medical abortion with misoprostol alone: from Latin America to the U.S. National Abortion Federation Annual Meeting, Boston, 2007 (panel presentation).

Women's perspectives on abortion: evidence from Latin America. National Abortion Federation Annual Meeting, Minneapolis, 2008 (panel presentation).

Provider perspective: What do clinicians and pharmacists think about OTC provision of OCs? Annual meeting of the American Public Health Association, San Diego, 2008 (invited talk).

Second trimester surgical and medical abortion in South Africa. Annual meeting of the National Abortion Federation, Portland, OR, 2009 (oral presentation)

Contraceptive knowledge and use among Latinas. Annual meeting of the National Abortion Federation, Portland, OR, 2009 (panel presentation).

National invited presentations (continued)

Self-induced abortion with misoprostol: from Latin America to the US. National Network of Abortion Funds Organizing Summit, Chicago, 2009 (invited talk).

Abortion self-induction among women living in San Francisco, Boston, New York City, and a border city in Texas: A qualitative analysis. Annual meeting of the American Public Health Association, Philadelphia, PA, 2009 (oral presentation).

Knowledge regarding oral contraceptive use, risks and benefits among clinic and pharmacy users in El Paso, Texas, and the impact of written information. Annual meeting of the American Public Health Association, Philadelphia, PA, 2009 (oral presentation).

Are women who obtain oral contraceptives over the counter in Mexico more likely to be contraindicated for use? Results from a cohort study in El Paso, Texas. Reproductive Health 2009, Los Angeles, CA, 2009 (oral presentation).

Evaluation of a program providing medication abortion via telemedicine in Iowa. Annual meeting of the National Abortion Federation, Philadelphia, 2010 (oral presentation). Received the Scientific Paper Award for this presentation.

Latinas' knowledge about abortion laws and services in San Francisco, Boston and New York City. Annual meeting of the American Public Health Association, Denver, CO, 2010 (oral presentation).

Regional and other invited presentations

Medical abortion with misoprostol alone: from Latin America to the Mission. Grand rounds presentation, Department of Obstetrics, Gynecology and Reproductive Sciences, UCSF, 2007.

The safety, efficacy and acceptability of over-the-counter provision of combined oral contraceptives. Grand rounds presentation, Department of Obstetrics, Gynecology and Reproductive Sciences, UCSF, 2007.

The safety, efficacy and acceptability of over-the-counter provision of combined oral contraceptives. Annual meeting of the Washington State Obstetrical Association, Seattle, 2008 (invited talk).

Self-induced abortion with misoprostol: from Latin America to the U.S. Grand rounds presentation in the Department of Obstetrics and Gynecology, University of Michigan School of Medicine, Ann Arbor, 2009 (invited talk).

OTHER PROFESSIONAL SERVICE

2007	Member of the International Planned Parenthood Federation Safe Abortion Action Fund Technical Review Panel (London)
2007-2009	Steering committee member of the California Microbicide Initiative
2002-2004	Member, Medical Development Team, Marie Stopes International (London)

TEACHING

FORMAL SCHEDULED CLASSES:

Qtr	Academic Yr	Institution Course Title	Teaching Contribution	Class Size
S	2004-05	Mexican National Institute for Public Health; Introduction to Reproductive Health	Lecturer; 2 lectures	20
S	2005-06	Harvard School of Public Health; PIH502 International reproductive health issues: Moving from theory to practice	Lecturer; 1 lecture	10
S	2006-07	Harvard School of Public Health; PIH502 International reproductive health issues: Moving from theory to practice	Lecturer; 2 lectures	15
S	2007-08	Harvard School of Public Health; PIH502 International reproductive health issues: Moving from theory to practice	Lecturer; 2 lectures	10
W	2008-09	Harvard School of Public Health; GHP502 International reproductive health issues: Moving from theory to practice	Lecturer; 2 lectures	22
W	2009-10	Harvard School of Public Health; GHP502 International reproductive health issues: Moving from theory to practice	Lecturer; 1 lecture	17

POSTGRADUATE and OTHER COURSES

Guest lecturer in "Qualitative Research Methods in Public Health," CUNY School of Public Health, September 2011

Women's health from a global perspective. Presentation at Obstetrics and Gynecology Update: What Does the Evidence Tell Us? (UCSF CME course organized by the Department of Obstetrics, Gynecology and Reproductive Sciences), San Francisco, 2007.

TEACHING AIDS

Contributed to the development of a training slide set on medical abortion in Spanish, 2004

Developed pocket cards on emergency contraception for use by community health workers in the State of Mexico, 2005

Reviewed and provided input on a manual on gynecologic uses of misoprostol published by the Latin American Federation of Obstetric and Gynecologic Societies (FLASOG), 2005

Grossman D. Medical methods for first trimester abortion: RHL commentary (last revised: 3 September 2004). The WHO Reproductive Health Library, No 8, Update Software Ltd, Oxford, 2005. Exerpt available at: http://www.rhlibrary.com/Commentaries/htm/Dgcom.htm.

TEACHING AIDS (continued)

Grossman D. Medical methods for first trimester abortion: RHL practical aspects (last revised: 3 September 2004). The WHO Reproductive Health Library, No 8, Update Software Ltd, Oxford, 2005.

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AWARDS AND GRANTS

CURRENT

1 R01 HD047816-01A1 (Co-PI) 09/01/05-06/30/11
NICHD
Oral Contraceptive Use along the US/Mexico Border

Research Award (Co-PI) 01/01/10-12/31/12
University of California at San Francisco (subcontract from grant from the Bill and Melinda Gates Foundation)
The Effect of Integrating Family Planning Services in the Context of HIV Care and Treatment in Nyanza Province, Kenya

Research Award (PI) 07/01/10-06/30/11
Anonymous donor
E-medicine provision of medical abortion

Research Award (Co-PI) 11/18/08-11/17/12
The William and Flora Hewlett Foundation
Planning grant for the OCs OTC working group

Research Award (Co-PI) 10/18/05-10/17/10
The William and Flora Hewlett Foundation
Ibis General Support

Research Award (Co-PI) 11/1/06-10/31/12
Anonymous donor
Reducing the effects of unsafe abortion in Latin America

Research Award SFP3-4 (PI) 09/01/09-08/31/11
Society of Family Planning
Cervical priming before D&E in South Africa

Research Award (PI) 06/01/07-08/31/11
The Wallace Alexander Gerbode Foundation
Reproductive health among Latinas
Barriers to reproductive health services among US military servicewomen

PAST (selected)

Research Award (PI) 08/01/07-06/30/10
IPPF Safe Abortion Action Fund
Improving second trimester abortion services in South Africa

PAST AWARDS (continued)

Research Award (Co-PI) 01/01/09-12/31/09
University of California at San Francisco (subcontract from grant from the Tides Africa Fund)
The Effect of Integrating Family Planning Services in the Context of HIV Care and Treatment in Nyanza Province, Kenya

Research Award SFP1-5 (PI) 09/01/07-04/30/09
Society of Family Planning
Abortion Self-induction Among Low-income Women in San Francisco, Boston and New York: A Quantitative and Qualitative Study

Research Award (Co-PI) 05/01/07-04/30/09
University of California at San Francisco (subcontract from grant from CDC, President's Emergency Plan for AIDS Relief)
The Effect of Integrating Family Planning Services in the Context of HIV Care and Treatment

Research Award (Clinical monitor) 10/2002-9/2007
University of California at San Francisco (Bill & Melinda Gates Foundation)
Preventing HIV by Protecting the Cervix: Re-examining the Diaphragm, an Inexpensive, Widely Available, Woman-Controlled, Physical Barrier of the Cervix.

Research Award (PI) 12/1/05-12/31/07
The Population Council
Acceptability of Female-Controlled Barrier Methods to Prevent Bacterial STIs Among Vulnerable Populations in the Dominican Republic

Research Award (Co- PI) 9/1/03-12/31/06
The Mary Wohlford Foundation
General Support

PEER REVIEWED PUBLICATIONS

1. Laudon M, Grossman DA, Ben-Jonathan N. Prolactin-releasing factor: cellular origin in the intermediate lobe of the pituitary. Endocrinology, 1990 Jun; 126(6):3185-92.
2. Grossman DA, Witham ND, Burr DH, Lesmana M, Rubin FA, Schoolnik GK, Parsonnet J. Flagellar serotypes of Salmonella typhi in Indonesia: relationships among motility, invasiveness, and clinical illness. Journal of Infectious Diseases, 1995 Jan; 171(1):212-6.
3. MacIsaac L, Grossman D, Balistreri E, Darney P. A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion. Obstetrics and Gynecology, 1999; 93(5, pt.1):766-770.
4. Weitz T, Foster A, Ellertson C, Grossman D, Stewart F. "Medical" and "surgical" abortion: rethinking the modifiers. Contraception 2004; 69(1):77-8.
5. Grossman D, Ellertson C, Grimes DA, Walker D. Routine follow-up visits after first-trimester induced abortion. Obstetrics and Gynecology 2004; 103(4):738-45.

PEER REVIEWED PUBLICATIONS (continued)

6. Lafaurie MM, Grossman D, Troncoso E, Billings DL, Chávez S. Women's perspectives on medical abortion in Mexico, Colombia, Ecuador and Peru: a qualitative study. Reproductive Health Matters 2005;13(26):75-83.
7. Grossman D, Ellertson C, Abuabara K, Blanchard K. Barriers to contraceptive use present in product labeling and practice guidelines. American Journal Public Health 2006;96(5):791-9.
8. Yeatman SE, Potter JE, Grossman DA. Over-the-counter access, changing WHO guidelines, and the prevalence of contraindicated oral contraceptive use in Mexico. Studies in Family Planning, 2006; 37(3):197–204.
9. Pace L, Grossman D, Chavez S, Tavara L, Lara D, Guerrero R. Legal Abortion in Peru: Knowledge, attitudes and practices among a group of physician leaders. Gaceta Medica de Mexico, 2006; 142(Supplement 2):91-5.
10. Lara D, Abuabara K, Grossman D, Diaz C. Pharmacy provision of medical abortifacients in a Latin American city. Contraception, 2006;74(5):394-9.
11. Tinajeros F, Grossman D, Richmond K, Steele M, Garcia SG, Zegarra L, Revollo R. Diagnostic accuracy of a point-of-care syphilis test when used among pregnant women in Bolivia. Sexually Transmitted Infections 2006;82 Suppl 5:v17-21.
12. Clark W, Gold M, Grossman D, Winikoff B. Can mifepristone medical abortion be simplified? A review of the evidence and questions for future research. Contraception 2007;75:245-50.
13. Garcia SG, Tinajeros F, Revollo R, Yam EA, Richmond K, Díaz-Olavarrieta C, Grossman D. Demonstrating public health at work: A demonstration project of congenital syphilis prevention efforts in Bolivia. Sexually Transmitted Diseases 2007;34(7):S37-S41.
14. Harper CC, Blanchard K, Grossman D, Henderson J, Darney P. Reducing Maternal Mortality due to Abortion: Potential Impact of Misoprostol in Low-resource Settings. International Journal of Gynecology and Obstetrics 2007;98:66-9.
15. Díaz-Olavarrieta C, Garcia SG, Feldman BS, Martinez Polis A, Revollo R, Tinajeros F, Grossman D. Maternal syphilis and domestic violence in Bolivia: A gender-based analysis of implications for partner notification and universal screening. Sexually Transmitted Diseases 2007;34(7):S42-S46.
16. Grossman D, Berdichevsky K, Larrea F, Beltran J. Accuracy of a semi-quantitative urine pregnancy test compared to serum beta-hCG measurement: a possible tool to rule-out ongoing pregnancy after medication abortion. Contraception 2007;76(2):101-4.
17. Lara D, van Dijk M, Garcia S, Grossman D. La introducción de la anticoncepción de emergencia en la norma oficial mexicana de planificación familiar (The introduction of emergency contraception into the official Mexican family planning norms). Gaceta Médica de México 2007;143(6): 483-7.
18. Grossman D, Blanchard K, Blumenthal P. Complications after second trimester surgical and medical abortion. Reproductive Health Matters 2008;16(31 Supplement):173-82.
19. Grossman D, Fernandez L, Hopkins K, Amastae J, Garcia SG, Potter JE. Accuracy of self-screening for contraindications to combined oral contraceptive use. Obstetrics and Gynecology 2008; 112(3):572-8.

PEER REVIEWED PUBLICATIONS (continued)

20. Grossman D. Should the oral contraceptive pill be available without prescription? Yes. British Medical Journal 2008;337:a3044.
21. Levin C, Grossman D, Berdichevsky K, Diaz C, Aracena B, Garcia S, Goodyear L. Exploring the economic consequences of unsafe abortion: implications for the costs of service provision in Mexico City. Reproductive Health Matters 2009;17(33):120–132.
22. Hu D, Grossman D, Levin C, Blanchard K, Goldie SJ. Cost-Effectiveness Analysis of Alternative First-Trimester Pregnancy Termination Strategies in Mexico City. BJOG 2009;116:768–779.
23. Goodman S, Gordon R, Eckhardt C, Osborne S, Grossman D, Spiedel JJ. Beyond education and training: making change stick. Contraception 2009;79(5):331-3.
24. Távara-Orozco L, Chávez S, Grossman D, Lara D, Blandón MM. Disponibilidad y uso obstétrico del misoprostol en los países de América [Availability and obstetric use of misoprostol in Latin American countries]. Revista Peruana de Ginecologia y Obstetricia 2009;54:253-263.
25. Lara DK, Grossman D, Muñoz J, Rosario S, Gomez B, Garcia SG. Acceptability and use of female condom and diaphragm among sex workers in Dominican Republic: Results from a prospective study. AIDS Education and Prevention 2009;21(6):538-551.
26. Grossman D, Fernandez L, Hopkins K, Amastae J, Potter JE. Perceptions of the safety of oral contraceptives among a predominantly Latina population in Texas. Contraception 2010;81(3):254-60. (NIHMS155993)
27. Potter JE, White K, Hopkins K, Amastae J, Grossman D. Clinic versus Over-the-Counter Access to Oral Contraception: Choices Women Make in El Paso, Texas. American Journal of Public Health 2010;100(6):1130-6. (NIHMS 221745)
28. Phillips K, Grossman D, Weitz T, Trussell J. Abortion coverage and health reform: bringing evidence to bear. Contraception 2010;82(2):129-30.
29. Hu D, Grossman D, Levin C, Blanchard K, Adanu R, Goldie SJ. Cost-Effectiveness Analysis of Unsafe Abortion and Alternative First-Trimester Pregnancy Termination Strategies in Nigeria and Ghana. African Journal of Reproductive Health 2010;14(2)85-103.
30. Grossman D, Holt K, Peña M, Veatch M, Gold M. Winikoff B, Blanchard K. Abortion self-induction in the US. Reproductive Health Matters 2010;18(36):136–146.
31. Grossman D, Grindlay K. Alternatives for follow-up after medication abortion: A systematic review. Contraception 2011;83(6):504-10.
32. Liang S-Y, Grossman D, Phillips K. Women's current out-of-pocket expenditures and dispensing patterns for oral contraceptives. Contraception 2011;83(6):528-36.
33. Blanchard K, Bostrom A, Montgomery E, van der Straten A, Lince N, de Bruyn G, Grossman D, Chipato T, Ranjee G, Padian N. Contraception use and effectiveness among women in a trial of the diaphragm for HIV prevention. Contraception 2011;83(6):556-63.
34. Grossman D, White K, Hopkins K, Amastae J, Shedlin M, Potter JE. Contraindications to Combined Oral Contraceptives Among Over-the-Counter versus Prescription Users. Obstet Gynecol 2011;117(3):558–65.

PEER REVIEWED PUBLICATIONS (continued)

35. Potter JE, McKinnon S, Hopkins K, Amastae J, Shedlin MG, Powers DA, Grossman D. Continuation of prescribed compared with over-the-counter oral contraceptives. Obstet Gynecol 2011;117(3):551–7.
36. Grindlay K, Yanow S, Jelinska K, Gomperts R, Grossman D. Abortion restrictions in the US military: Voices from women deployed overseas. Women's Health Issues 2011;21(4):259-64.
37. Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and Acceptability of Medical Abortion Provided Through Telemedicine. Obstetrics and Gynecology 2011;118(2 Pt 1):296-303.
38. Holt K, Grindlay K, Taskier M, Grossman D. Unintended pregnancy and contraceptive use among women in the US military: A systematic literature review. Military Medicine 2011;176(9):1056-64.
39. Harris LH, Grossman D. Confronting the challenge of unsafe second-trimester abortion. Int J Gynaecol Obstet 2011;115(1):77-9.
40. Grossman D. Over-the-counter access to oral contraceptives. Expert Review of Obstetrics and Gynecology 2011; 6(5):501-8.
41. Grossman D, Constant D, Lince N, Alblas M, Blanchard K, Harries J. Surgical and medical second trimester abortion in South Africa: a cross-sectional study. BMC Health Serv Res. 2011;11(1):224.
42. Foster DG, Higgins J, Karasek D, Ma S, Grossman D. Attitudes toward unprotected intercourse and risk of pregnancy among women seeking abortion. In press at Women's Health Issues.
43. Foster DG, Karasek D, Grossman D, Darney P, Schwarz EB. Interest in using intrauterine contraception when the option of self-removal is provided. In press at Contraception.

NON-PEER REVIEWED PUBLICATIONS

Review articles

1. Levin C, Grossman D, Garcia SG. Unsafe abortion costs in Mexico City. In: Institute of Development Studies. id2 health focus: unsafe abortion. 2007.
2. Grossman D. Should oral contraceptives be sold over-the-counter? Yes. Contemporary OB/GYN 2008;53(9):63-73.

Book and chapters

1. Grossman D, Díaz Olavarrieta C. Manejo del dolor en la atención posaborto (Pain management in the post-abortion care setting). In: Billings DL, Vernon R. Avances en la atención posaborto en América Latina y el Caribe: Investigando, aplicando y expandiendo. Mexico City: The Population Council. 2007.
2. Lafaurie MM, Grossman D, Troncoso E, Billings DL, Chávez S, Maira G, Martinez I, Mora M, Ortiz O. El aborto con medicamentos en América Latina: Las experiencias de las mujeres en México, Colombia, Ecuador y Perú. Bogota, 2005.

Other publications

1. Grossman D. Medical methods for first trimester abortion: RHL commentary (last revised: 3 September 2004). The WHO Reproductive Health Library, No 8, Update

Software Ltd, Oxford, 2005. Exerpt available at: http://www.rhlibrary.com/Commentaries/htm/Dgcom.htm.

2. Grossman D. Medical methods for first trimester abortion: RHL practical aspects (last revised: 3 September 2004). The WHO Reproductive Health Library, No 8, Update Software Ltd, Oxford, 2005.
3. Potter JE and Grossman D. Make birth control available to immigrants. Op-ed in the Austin Statesman 2010. Available at http://www.statesman.com/opinion/potter-grossman-make-birth-control-available-to-immigrants-896651.html.
4. Grossman D. Female active duty soldiers face many barriers to care. RH Reality Check 2010. Available at: http://www.rhrealitycheck.org/blog/2010/12/08/study-female-active-duty-soldiers-face-many-barriers-care.

LANGUAGES

Fluent in Spanish, conversant in French.

Exhibit B

ACOG
PRACTICE
BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR
OBSTETRICIAN–GYNECOLOGISTS

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This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Mitchell D. Creinin, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Medical Management of Abortion

Over the past two decades, medical methods of abortion have been developed throughout the world and are now used in the United States. Medical abortion, which involves the use of medications to induce an abortion rather than a surgical abortion, is an option for women who wish to terminate a pregnancy up to 63 days of gestation (calculated from the first day of the last menstrual period). Medical abortions currently account for 6% of all abortions in the United States (1). The purpose of this document is to present evidence of the effectiveness, benefits, and risks of medical abortion and provide a framework for the evaluation and counseling of women who are considering medical abortion.

Background

Medications Currently Used in Medical Abortion

Mifepristone

Mifepristone (RU-486), a derivative of norethindrone, binds to the progesterone receptor with an affinity greater than progesterone but does not activate the receptor, thereby acting as an antiprogestin (2). Mifepristone's known actions on a pregnant uterus include necrotizing the decidua, softening the cervix, and increasing both uterine contractility and prostaglandin sensitivity (3, 4). Human studies have suggested that uterine contractility does not increase until 24–36 hours after mifepristone administration (4). At this point, the myometrium is five times more sensitive to the stimulatory effects of exogenous prostaglandins (4).

Administration of mifepristone followed by a prostaglandin analogue, usually misoprostol, is the most commonly used medical abortion regimen throughout the world. As a progesterone receptor antagonist, mifepristone also has several other potential medical applications, including emergency contraception, cervical ripening for labor induction, and treatment of conditions

such as symptomatic leiomyomata uteri, endometriosis, Cushing's syndrome, breast cancer, and glaucoma.

Misoprostol

Misoprostol is an inexpensive prostaglandin analogue in a tablet form that is stable at room temperature. Misoprostol is used clinically for prevention of gastric ulcers in individuals taking antiinflammatory drugs on a long-term basis, for abortion, and for labor induction. Pharmacokinetic evaluation of oral and vaginal administration of misoprostol demonstrates that oral misoprostol is absorbed more rapidly, resulting in a higher peak serum level (5, 6), but vaginal administration results in greater uterine contractility. Recent evaluations of sublingual administration show higher peak serum concentrations (7, 8), which may result in more unnecessary side effects (7). Further study of buccal administration may be warranted because its pharmacokinetic profile appears to be similar to vaginal administration (7).

Other Agents

Methotrexate is used less often today for medical abortion because of the greater availability of mifepristone. Methotrexate blocks dihydrofolate reductase, an enzyme involved in producing thymidine during DNA synthesis. Methotrexate exerts its action primarily on the cytotrophoblast rather than the developing embryo. Methotrexate has been used for more than 40 years to treat neoplastic diseases, rheumatoid arthritis, and psoriasis; other medical applications include treatment of systemic lupus erythematosus, dermatomyositis, severe asthma, Crohn's disease, and extrauterine pregnancy.

Tamoxifen has been used in combination with misoprostol in some studies of early abortion. However, randomized trials have demonstrated no benefit of using a tamoxifen–misoprostol regimen compared with a methotrexate–misoprostol regimen (9) or misoprostol alone (10).

Mifepristone Regimens

Protocol Approved by the U.S. Food and Drug Administration

Mifepristone regimens vary according to dosage, timing, and route of administration (see Table 1). The U.S. Food and Drug Administration (FDA) approved the protocol of mifepristone, 600 mg orally, followed approximately 48 hours later by misoprostol, 400 µg orally. This is safe and effective for medical abortion through 49 days of gestation (calculated from the first day of the last menstrual period [LMP]). A follow-up evaluation is scheduled approximately 14 days after administration of mifepristone. At that time, if clinical history and physical examination do not confirm expulsion, ultrasonography is performed. If a gestational sac is seen, aspiration is typically performed.

Efficacy with this regimen is approximately 92% in women with pregnancies up to 49 days of gestation (11, 12). Complete abortion rates are higher with earlier gestations: approximately 96–98% for pregnancies up to 42 days of gestation (13, 14), 91–95% from 43 to 49 days of gestation (13, 14), and less than 85% beyond 49 days of gestation (11, 13, 14).

Alternative Regimens

Other evidence-based medical abortion regimens have been developed in an effort to reduce side effects and to make medical abortion less expensive, safer, and more rapid. Regimens using 200-mg doses of mifepristone orally have efficacy rates comparable to the FDA-approved regimen (12, 15) at one third of the cost. Additionally, increasing the misoprostol dose to 800 µg and administering the medication vaginally decreases the time to expulsion (16), results in fewer side effects (16, 17), and improves complete abortion rates when compared with oral administration of a 400-µg dose of misoprostol (16, 18–20). Multiple large studies in the United States have demonstrated that a patient can safely and effectively self-administer the misoprostol (orally or vaginally) in her home (18, 19, 21–27).

Investigations also have demonstrated the flexibility in timing between the two medications. One study demonstrated that 800 µg of misoprostol may be administered either 24, 48, or 72 hours after 200 mg of mifepristone with equal efficacy in pregnancies up to 56 days of gestation (23); a follow-up study using a regimen with a 24-hour interval between medications yielded similar results in pregnancies up to 63 days of gestation (24). Moreover, the results of a randomized multicenter study indicated that 800 µg of misoprostol administered vaginally 6–8 hours after 200 mg of mifepristone resulted in significantly fewer side effects (and no decrease in efficacy) than regimens using a 24-hour interval (27).

Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using mifepristone, 200 mg orally, and misoprostol, 800 µg vaginally, are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.

Nonmifepristone Regimens

Methotrexate and Misoprostol

The combination of methotrexate and misoprostol is an alternative early medical abortion regimen. Among

Table 1. Comparison of Common Medical Abortion Regimens

Common Regimens	Overall Success Rate (%)	Advantages and Disadvantages	Gestational Age
Mifepristone, 600 mg orally + misoprostol, 400 µg orally (FDA-approved regimen)	92[a]	Must remain in office or clinic 4 hours after administration	Up to 49 days
Mifepristone, 200 mg orally + misoprostol, 800 µg vaginally (alternative evidence-based regimen)	95–99[b–i]	Compared with FDA-approved regimen: • More effective • Less time to expulsion • Fewer side effects • Requires vaginal administration of a medication	Up to 63 days
Methotrexate, 50 mg/m² IM or 50 mg vaginally, + misoprostol, 800 µg vaginally 3–7 days later	92–96[g–i]	Compared with mifepristone–misoprostol regimen: • Takes longer for expulsion in 20–30% of women • Readily available medications • Low drug cost	Up to 49 days
Misoprostol only, 800 µg vaginally repeated for up to three doses	88[j]	• Requires complicated dosing regimens • Significantly higher incidence of side effects than other regimens • Low drug cost	Up to 56 days

Abbreviations: FDA, U.S. Food and Drug Administration; IM, intramuscularly

[a]Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998;338:1241–7.

[b]Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. Contraception 1999;59:1–6.

[c]Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. Contraception 2001;64:81–5.

[d]el-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. N Engl J Med 1995;332:983–7.

[e]von Hertzen H, Honkanen H, Piaggio G, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, et al. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. WHO Research Group on Post-Ovulatory Methods for Fertility Regulation. BJOG 2003;110:808–18.

[f]Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. MOD Study Trial Group. Obstet Gynecol 2004;103:851–9.

[g]Creinin MD, Vittinghoff E, Schaff E, Klaisle C, Darney PD, Dean C. Medical abortion with oral methotrexate and vaginal misoprostol. Obstet Gynecol 1997;90:611–6.

[h]Creinin MD, Carbonell JL, Schwartz JL, Varela L, Tanda R. A randomized trial of the effect of moistening misoprostol before vaginal administration when used with methotrexate for abortion. Contraception 1999;59:11–6.

[i]Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. Obstet Gynecol 2002;99:813–9.

[j]Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell DR Jr. A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Hum Reprod 2002;17:1477–82.

women with pregnancies up to 49 days of gestation, this regimen results in a complete abortion rate of 92–96%. Between 50 days and 56 days of gestation, however, efficacy decreases to 82% (28). Although overall efficacy is equal to the standard regimen of mifepristone–misoprostol, approximately 15–25% of women using methotrexate regimens may wait up to 4 weeks for complete abortion to occur (25, 29, 30).

Methotrexate is most commonly administered intramuscularly at a dose based on body surface area (50 mg/m²), the same dose used for the management of ectopic pregnancy (31). However, regimens using 50 mg of methotrexate orally appear to be as effective as those using methotrexate, 50 mg/m² intramuscularly (29, 32, 33). Misoprostol (800 µg) is administered by the woman 3–7 days later at home. A follow-up examination is performed approximately 1 week after methotrexate administration; a vaginal ultrasound examination is performed to confirm passage of the gestational sac. If abortion has not occurred, the misoprostol dose is repeated. Further follow-up for women requiring a second dose of misoprostol is performed in 4 weeks unless embryonic cardiac activity is still visible on ultrasound examination, in which case patients return in 1 week. If gestational cardiac activity is present 2 weeks after initiating treatment or expulsion has not occurred by the 4-week follow-up visit, aspiration is performed.

Misoprostol Alone

Misoprostol, 800 µg vaginally, when moistened with water, can result in complete abortion rates of 90% in women with pregnancies up to 56 days of gestation

(10, 34–38). Studies with nonmoistened vaginal misoprostol demonstrated lower rates of 50–67% (39–41). Studies showing that misoprostol alone is effective for abortion often involve complex dosing regimens or require clinician application of the tablets. Additionally, this treatment results in significantly higher rates of side effects (nausea, vomiting, diarrhea, and fever and chills) than those using misoprostol after pretreatment with either mifepristone or methotrexate (10, 34–37). Recent trials with sublingual misoprostol in repeated doses do not appear to improve outcome over vaginal misoprostol and may cause even more side effects (38, 42).

A recent randomized, double-blind trial in women with pregnancies up to 56 days of gestation compared a misoprostol-only regimen (800 μg vaginally) with a regimen of 200 mg of mifepristone orally followed 48 hours later by 800 μg of misoprostol vaginally (43). In both groups, misoprostol was repeated every 24 hours for up to three doses. Complete abortion rates for each regimen were 88.0% and 95.7%, respectively ($P<.05$). The women who received mifepristone aborted much more quickly and required fewer doses of misoprostol compared with women who received misoprostol alone.

Mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally generally are preferred to regimens using methotrexate and misoprostol or misoprostol only for medical abortion.

Counseling Patients

Medical Versus Surgical Abortion

Patient counseling must first include discussion of pregnancy options to be sure that a woman is certain about her decision to have an abortion. If she is uncertain, the decision about abortion technique must be delayed until she has reached a firm decision, even if the delay means that she will be unable to choose a medical option. It is important to respect the patient's autonomy and to separate the decision to terminate the pregnancy from the decision about the method to be used.

After a woman has considered her options and has decided to have an abortion, the method must be selected. Most women seeking early abortion will be eligible for both medical and surgical methods. Medical abortion should be considered a medically acceptable alternative to surgical abortion in selected, carefully counseled, and informed women. The general advantages and disadvantages of each approach (Table 2) should be explained early in the counseling process because most women will have a clear preference (44, 45). Even among women who think they are unsure, most will have some preference after counseling (44).

Table 2. Features of Medical and Surgical Abortion

Medical Abortion	Surgical Abortion
• Usually avoids invasive procedure	• Involves invasive procedure
• Usually avoids anesthesia	• Allows use of sedation if desired
• Requires two or more visits	• Usually requires one visit
• Days to weeks to complete	• Complete in a predictable period of time
• Available during early pregnancy	• Available during early pregnancy
• High success rate (~95%)	• High success rate (99%)
• Bleeding moderate to heavy for short time	• Bleeding commonly perceived as light
• Requires follow-up to ensure completion of abortion	• Does not require follow-up in all cases
• Patient participation throughout a multiple-step process	• Patient participation in a single-step process

Adapted from Breitbart V. Counseling for medical abortion. Am J Obstet Gynecol 2000;183:S26–33.

Counseling and Symptom Management

Some degree of bleeding and uterine cramping are necessary for the medical abortion process to occur. Other potential side effects of medical abortion include nausea, vomiting, diarrhea, warmth or chills, headache, dizziness, and fatigue (Table 3). Counseling should emphasize that bleeding may be much heavier than menses, potentially with severe cramping. The woman should understand how much bleeding is considered too much. An easy reference for the patient to use is soaking of two pads per hour for 2 hours in a row (46). This is not necessarily a point at which intervention is needed but a time when the woman should call the health care provider. Whether or not it is imperative for the patient to seek emergency care depends on how she is feeling, her baseline hemoglobin, whether the bleeding seems to be slowing, and how far she is from an emergency treatment facility.

Pain management is especially important for the woman aborting at home. She should be sent home with appropriate instructions for analgesia with over-the-counter medications, as well as with prescriptions for oral narcotics to use if needed.

The incidence of each symptom will depend on the regimen used, the dose and route of administration of the prostaglandin analogue, and gestational age. Gastrointestinal side effects are less common when dry misoprostol is administered vaginally compared with regimens that use oral misoprostol or moistened vaginal misoprostol. Oral ulcers with methotrexate use, although rare, have been reported in the literature.

Table 3. Incidence of Side Effects in Selected North American Trials of Medical Abortion Regimens*

	Incidence of Side Effects (%)											
	Nausea		Vomiting		Diarrhea		Headache		Dizziness		Thermoregulatory†	
Trial	Mife	Miso	Mife	Miso	Mife	Miso	Mife	Miso	Mife	Miso	Mife	Miso
Schaff et al (1997)‡	36	36	14	14	8	22	18	19	22	37	20	37
Schaff et al (1999)§	45	43	13	26	11	23	14	13	15	28	14	32
Wiebe et al (2002)‖	45	39	13	15	5	16	19	29	NR	NR	NR	23
Creinin (2004)¶	20	44	5	23	1	27	10	37	12	35	9	56
Creinin (2004)#	39	52	14	30	7	25	20	37	20	37	19	53

Abbreviations: Mife, mifepristone; Miso, misoprostol; NR, not reported

*Studies are included only if the incidences of side effects were differentiated between the medications.

†Fever, warmth, hot flashes, or chills

‡Mifepristone, 600 mg, followed by misoprostol, 800 µg vaginally, 36–48 hours later. (Schaff EA, Stadalius LS, Eisinger SH, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. J Fam Pract 1997;44:353–60.)

§Mifepristone, 200 mg, followed by misoprostol, 800 µg vaginally, 48 hours later. (Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. Contraception 1999;59:1–6.)

‖Mifepristone, 600 mg, followed by misoprostol, 400 µg orally, 36–48 hours later. (Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. Obstet Gynecol 2002;99:813–9.)

¶Mifepristone, 200 mg, followed by misoprostol, 800 µg vaginally, 6–8 hours later (first row). (Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004;103:851–9.)

#Mifepristone, 200 mg, followed by misoprostol, 800 µg vaginally, 23–25 hours later (second row). (Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004;103: 851–9.)

Need for Follow-up Dilation and Curettage

A failed medical abortion is defined as the presence of gestational cardiac activity on vaginal ultrasonography 2 weeks after the initiation of treatment. No studies have assessed the efficacy of additional doses of mifepristone, methotrexate, or misoprostol after a medical abortion failure. Continuing pregnancies, which should be terminated by surgical evacuation, are typically reported in less than 1% of women who begin treatment at 49 days of gestation or less regardless of regimen.

Intervention guidelines vary for women who have a persistent gestational sac seen on ultrasonography without evidence of embryonic cardiac activity or continuing development. Typically, protocols used in mifepristone studies define a retained sac 2 weeks after the administration of mifepristone as an indication for suction evacuation. However, medical abortion studies using methotrexate and misoprostol demonstrate that intervention for a nonviable pregnancy is unnecessary and that expulsion will occur, on average, between 22 and 29 days after the methotrexate is administered (28, 29, 40, 47, 48). With this understanding, the mifepristone studies performed in the United States over the past 6 years have allowed approximately 36 days to elapse after mifepristone administration before recommending surgical intervention (18, 19, 22–25, 27). Most commonly, a woman who has not aborted and is awaiting delayed expulsion will no longer feel pregnant or have medication-induced symptoms; the patient will be waiting for the onset of bleeding or cramping similar to anticipating the start of menses (28). Providers must differentiate this scenario from women who have incomplete expulsion of the pregnancy tissue, for whom symptoms can include prolonged and irregular bleeding episodes. Early trials of methotrexate and misoprostol showed that serial β-hCG evaluations did not aid in the diagnosis of incomplete abortion. All women with an incomplete abortion presented clinically, and the incomplete abortion was not diagnosed by increasing or plateaued β-hCG levels (40, 49, 50).

Understanding the difference between incomplete abortion and the normal course of medical abortion is important. The sole purpose of ultrasound examination after misoprostol administration is to determine whether the gestational sac is present. After expulsion, the uterus will normally contain ultrasonographically hyperechoic tissue consisting of blood, blood clots, and decidua. Rarely does this finding during medical abortion indicate a need for intervention. In the absence of excessive bleeding, providers can follow such patients conservatively (51).

Overall, large studies demonstrate that less than 1% of women undergoing medical abortion will need emergent curettage because of excessive bleeding

(13, 22, 52–54). Moreover, the risk of clinically significant bleeding and transfusion may be lower in women with pregnancies up to 49 days of gestation compared with those beyond 49 days (11); this relative risk will vary depending on the regimen used. Still, just as for women undergoing surgical abortion, surgical curettage must be available on a 24-hour basis for cases of hemorrhage. Clinicians who wish to provide medical abortion services either should be trained in surgical abortion or should work in conjunction with a clinician who is trained in surgical abortion.

Clinical Considerations and Recommendations

▶ ***What factors determine whether a woman is a candidate for medical abortion?***

Gestational Age

The upper limit of gestational age at which a medical abortion regimen is still an option varies depending on the types, dosages, and routes of administration of the medications. Outpatient treatment with mifepristone–misoprostol regimens up to 63 days of gestation and for methotrexate–misoprostol regimens up to 49 days of gestation are highly effective. Complete abortion rates among all regimens are highest for earlier gestations and are clinically similar in women with pregnancies up to 49 days of gestation. Between 50 and 63 days of gestation, the use of vaginal misoprostol in regimens with mifepristone results in complete abortion in 96–99% of women (18, 22–24, 26, 27, 43, 53, 55), whereas regimens using oral misoprostol demonstrate significantly lower success rates for these gestational ages.

Contraindications

Medical contraindications to abortion with mifepristone regimens include confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass, intrauterine device in place, current long-term systemic corticosteroid therapy, chronic adrenal failure, severe anemia, known coagulopathy or anticoagulant therapy, and mifepristone intolerance or allergy. Most clinical trials also exclude women with severe liver, renal, or respiratory disease, uncontrolled hypertension, cardiovascular disease (angina, valvular disease, arrhythmia, or cardiac failure), or severe anemia. Misoprostol should not be used in women with an uncontrolled seizure disorder or those who have an allergy or intolerance to misoprostol or other prostaglandins. Asthma is not a contraindication because misoprostol is a weak bronchodilator.

Although medical contraindications are infrequent, social or psychologic contraindications to medical abortion are more common. Women are not good candidates for medical abortion if they do not wish to take responsibility for their care, are anxious to have the abortion over quickly, cannot return for follow-up visits, or cannot understand the instructions because of language or comprehension barriers. Other nonmedical criteria to be considered are access to a phone in case of an emergency and access to 24-hour emergency medical treatment (eg, surgical curettage for hemorrhage). Counseling should include a description of cramping and bleeding and should indicate that, rarely, the process may not be completed for several weeks.

▶ ***Which pretreatment laboratory tests are needed?***

No special pretreatment laboratory tests are necessary for medical abortion beyond those for surgical abortion. Confirmation of pregnancy by ultrasonography or pregnancy testing is necessary before attempting abortion regardless of method. Pretreatment assessment of hemoglobin or hematocrit and blood typing are imperative, and anti-D immune globulin should be administered if indicated.

▶ ***What is the risk of infection with medical abortion?***

Endometritis is a rare complication of medical abortion. In trials involving more than 500 participants, infection rates typically vary from 0.09% to 0.6% (11, 17, 18, 22, 23, 27, 56, 57). No data exist to support the universal use of prophylactic antibiotics for medical abortion. Five cases of death have been reported in women using mifepristone, 200 mg, followed by misoprostol, 800 µg vaginally, in North America since 2001; all appear to be infectious, with *Clostridium sordellii* identified in three of the cases (58). The cause of these infections and the relationship of the deaths to mifepristone and misoprostol are still under investigation. Even if related, the death rate would be less than 1 per 100,000 mifepristone procedures, a rate comparable to that for early surgical abortion and miscarriage (59).

▶ ***Is ultrasonography useful in the medical management of abortion before treatment?***

Gestational age should be confirmed by clinical evaluation or ultrasonography. Only 85% of U.S. women are able to predict gestational age within 2 weeks of the gestational age assigned by the clinician using ultrasound examination (60). Additionally, medical abortion studies in U.S. women have found that the gestational age determined by LMP was confirmed for only 40–60% of study

participants (14, 27, 61). Because efficacy for some regimens decreases significantly with increasing gestational age, the clinical relevance of erroneous gestational age assignment will vary according to the regimen used.

Although not required, all major U.S. trials of mifepristone or methotrexate have relied on transvaginal ultrasonography for dating and follow-up. In France, however, clinicians use ultrasonography for preabortion screening only when they find a discrepancy between uterine size and dating by LMP and when patients present with bleeding or symptoms suggestive of ectopic pregnancy. Pregnancy termination services in France are offered only by authorized abortion clinics staffed by highly experienced providers. The high efficacy and safety results in the French trials suggest that this selective use of ultrasonography suffices when medical abortion is provided by experienced clinicians.

A concern when providing early abortion services is the possibility of an undiagnosed extrauterine gestation. Although the ectopic pregnancy rate in the general population is currently around 19–21 per 1,000 pregnancies (62, 63), ectopic pregnancy rates in studies of women seeking abortion are consistently lower. A study of surgical abortion in women with pregnancies less than 42 days of gestation in the United States found the ectopic pregnancy rate to be 5.9 per 1,000 pregnancies (64). Similarly, the largest published study of medical abortion involved 16,369 women with pregnancies up to 49 days of gestation, 21 of whom were excluded from the analysis because of an ectopic pregnancy, yielding an ectopic pregnancy rate of 1.3 per 1,000 pregnancies (57). Although ectopic pregnancy in a population of women seeking early abortion is rare, women with significant medical risk factors or history (eg, unilateral pain and vaginal bleeding) should have pretreatment ultrasonography.

▶ *What methods can be used to confirm complete abortion?*

Transvaginal ultrasonography offers an efficient means of assessing outcome in patients who undergo medical abortion. Its primary objective is to determine if the gestational sac is absent (with or without the presence of other ultrasonographically hyperechoic tissue). However, French clinicians, who have extensive experience with medical abortion, use ultrasonography significantly less than American clinicians (65). One explanation for this difference may be less familiarity with the process by both American clinicians and patients; another reason could be liability concerns in the United States. A study of U.S. providers indicated that ultrasonography is perceived to be unnecessary to assess abortion outcome for most women (66). Researchers asked physicians if they felt comfortable with their assessment without ultrasonography or if they would feel better in that situation with an ultrasound examination to confirm their impression based on the patient's history and physical examination. Physicians thought an ultrasound examination was not needed in 60% of the women who were ultimately found to have expelled the gestational sac. However, the gestational sac was still present in 29% of women for whom physicians believed ultrasonography was not indicated.

Methods to verify abortion include reports of bleeding combined with evidence of uterine involution on pelvic examination or hCG testing. When misoprostol is administered 2–5 days after methotrexate or mifepristone, β-hCG concentrations should decrease by at least 50% within 1 week of initiating the medication regimen. However, performing sensitive serum or urine hCG assays (detection threshold, 25–50 mIU/mL) too soon after the termination of a pregnancy may result in an erroneous diagnosis of failed medical abortion. Two trials using methotrexate and misoprostol found that the average time to disappearance of β-hCG is 33–34 days and may take as long as 90 days (40, 67). The utility of nonsensitive urine hCG assays in follow-up after mifepristone and misoprostol administration warrants investigation.

In clinical trials with methotrexate and misoprostol, only about half of the women who thought they had aborted actually had done so (28). Moreover, women may experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac (28), or even an ectopic pregnancy (22). The importance of patient follow-up must be emphasized because failure rates for medical abortion are higher than those for surgical techniques.

However, recent data suggest that for most women having an abortion with mifepristone and misoprostol, no follow-up may be needed other than a telephone conversation. One report compared clinicians' and patients' impressions of whether or not expulsion occurred based solely on the patient's history with the results of vaginal ultrasonography performed approximately 1 week after initiating treatment (68). When the clinician and the patient both thought that expulsion had occurred, they were correct 99% of the time. Additional studies are needed to validate the premise that such women need only a home pregnancy test for follow-up and that office evaluation should be required only if either the clinician or the patient is not certain that expulsion has occurred.

▶ *Do nonsteroidal antiinflammatory drugs affect the success rates for medical abortion?*

Cramping pain for patients who are not undergoing abortion usually is treated with ibuprofen or other non-

steroidal antiinflammatory drugs (NSAIDs). Although NSAIDs inhibit the synthesis of new prostaglandins, they do not block the action of prostaglandin receptors; therefore, such agents should not inhibit the action of a prostaglandin used for medical abortion. The only report to evaluate the effects of analgesics on abortion outcome was a retrospective analysis of NSAIDs and complete abortion in 416 women who received misoprostol following methotrexate for medical abortion of pregnancies up to 56 days of gestation (69). The use of ibuprofen did not seem to interfere with the action of misoprostol to induce uterine contractions and pregnancy expulsion. Therefore, NSAIDs such as ibuprofen are not contraindicated for women undergoing a medical abortion.

▶ *How should a patient be counseled about potential teratogenicity if a medical method fails to lead to abortion?*

Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be informed of the need for a surgical abortion in the event of a continuing pregnancy. There is no evidence to date of a teratogenic effect of mifepristone. However, methotrexate is an antimetabolite that can cause fetal anomalies (70, 71). Evidence suggests that misoprostol also can result in congenital anomalies when used during the first trimester, possibly due to mild uterine contractions resulting in decreased blood flow during organogenesis (72). Anomalies associated with misoprostol use that have been described in the literature include defects in the frontal or temporal bones (73) and limb abnormalities with or without Möbius sequence (masklike facies with bilateral sixth and seventh nerve palsy and frequently coincident micrognathia) (74–77). No conclusions regarding teratogenicity can be drawn from these reports because of the extremely small sample sizes.

▶ *Does medical abortion affect future fertility?*

Future fertility following medical abortion has been evaluated only within a 1-year period after medical abortion in a group of 93 women who received methotrexate and misoprostol for abortion (78). Although none of the women were actively attempting to achieve pregnancy, 25% became pregnant, a rate higher than would be expected for a group of women using contraception. By comparison, another report indicated a pregnancy rate of 13% within 1 year after a first surgical abortion (79).

Summary of Recommendations and Conclusions

The following recommendations are based primarily on good and consistent scientific evidence (Level A):

- Medical abortion should be considered a medically acceptable alternative to surgical abortion in selected, carefully counseled, and informed women.
- The FDA-approved protocol of 600 mg of mifepristone orally followed approximately 48 hours later by 400 μg of misoprostol orally is safe and effective for medical abortion through 49 days of gestation (calculated from the first day of the LMP).
- Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.
- A methotrexate–misoprostol regimen is appropriate for medical abortion only in pregnancies up to 49 days of gestation. Women using this regimen may wait up to 4 weeks for complete abortion to occur.
- Mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally are generally preferred to regimens using methotrexate and misoprostol or misoprostol only for medical abortion.
- A patient can administer misoprostol safely and effectively, orally or vaginally, in her home as part of a medical abortion regimen.

The following recommendations are based primarily on limited scientific evidence (Level B):

- Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be informed of the need for a surgical abortion in the event of a failed abortion.
- Gestational age should be confirmed by clinical evaluation or ultrasonography.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Surgical curettage must be available on a 24-hour basis for cases of hemorrhage, even though less than

1% of women having a medical abortion will need a curettage because of excessive bleeding.

- Pretreatment anti-D immune globulin should be administered if indicated.
- No data exist to support the universal use of prophylactic antibiotics for medical abortion.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and June 2005. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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Appendix 5

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of its members, ET AL.,	)	
Plaintiffs,	)	Case No. CV-2011-1722
v.	)	
TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health, ET AL.,	)	Judge Daniel L. Owens
Defendants.	)	

DECLARATION OF DANA STONE, M.D. IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

DANA STONE, M.D., declares, under penalty of perjury, that the following statements are true and correct:

1. I provide the following facts and opinions as an expert in obstetrics and gynecology and the treatment of ectopic pregnancy. I have been licensed to practice medicine in the State of Oklahoma since 1991. My specialty is obstetrics and gynecology ("ob/gyn"). I provide a range of ob/gyn care for patients in my private practice, including treatment of patients with ectopic pregnancy. A copy of my curriculum vitae, which summarizes my background and experience, is attached hereto as Exhibit A.

2. An ectopic pregnancy occurs when a fertilized egg implants somewhere other than a woman's uterus. The overwhelming majority of ectopic pregnancies are located in a woman's fallopian tube. A tubal ectopic pregnancy can never result in a live birth.

3. Ectopic pregnancy can severely compromise a woman's health and can result in her death. Without treatment, the fertilized egg will continue to grow, in some cases causing damage to surrounding tissue. At some point, the ectopic pregnancy will become too big for the surrounding tissue to contain it, and it will rupture, potentially causing serious blood loss and/ or damage to internal organs, and threatening the woman's life.

4. It is possible to detect and treat a woman's ectopic pregnancy before it creates an immediate risk to her health or life. Early treatment of an ectopic pregnancy minimizes the risk of damage to surrounding tissue and rupture. It also helps to preserve a woman's chance of having future healthy pregnancies.

5. Once ectopic pregnancy is diagnosed, the standard of care is to provide treatment as soon as possible.

6. For some women with ectopic pregnancy, an intramuscular injection of the cancer drug methotrexate is a good treatment option. Methotrexate works by blocking the ability of folic acid to be used in cells. This prevents cells from growing normally, ending the pregnancy.

7. Methotrexate has not been approved by the United States Food and Drug Administration for its use in treating patients with ectopic pregnancy.

8. Medical research has proved that methotrexate is a safe, effective, and non-invasive way to treat patients with ectopic pregnancy. I offer methotrexate as a treatment option, for appropriate candidates, in my medical practice. When I'm providing treatment for a woman with tubal ectopic pregnancy, one of my goals is to provide care in a way that leaves her tube open and functional so that she can get pregnant again. That's exactly what the option of treating a patient with an injection of methotrexate does.

9. To be a good candidate for treatment with methotrexate, a patient needs to be in an early stage of ectopic pregnancy; in stable medical condition, not actively losing blood; and not

in severe pain. For those candidates, the standard of care requires physicians to offer methotrexate as a treatment option.

10. Methotrexate is the only non-surgical treatment option for women with ectopic pregnancy. It has at least two major advantages over surgery for a woman who is a good candidate: it shields her from the risks of surgery, and it preserves her fallopian tube. The risks of surgery for ectopic pregnancy include, among other things, damage to internal organs; damage to blood vessels requiring transfusion; and infection. Because such surgery requires general anesthesia, it also entails the risks of respiratory problems, heart attack, and stroke. In some cases, surgical management of a woman's ectopic pregnancy will compromise her future fertility.

11. In addition, some women with ectopic pregnancy have other medical conditions that increase the risk or complexity of surgical treatment, which makes methotrexate a particularly good option if they meet the criteria for it. For example, assuming the criteria for methotrexate are met, surgery would be disfavored as a treatment option for patients with a history of endometriosis, pelvic infection and/or multiple surgeries, any of which can create a buildup of scar tissue that makes surgery more difficult.

12. It is not good medical practice to do surgery unnecessarily. If a woman with ectopic pregnancy is a good candidate for methotrexate, there is no medical justification for depriving her of that treatment option.

13. If Oklahoma House Bill 1970 goes into effect, the result would be a huge loss for women's health in this state. Prohibiting off-label use of methotrexate would require Oklahoma physicians like myself to practice outside of the accepted standards of medical care for treatment of ectopic pregnancy.

Executed: January 24, 2012

DANA STONE, M.D.

Exhibit A

Curriculum Vitae
Dana Gail Stone, M.D.

Personal

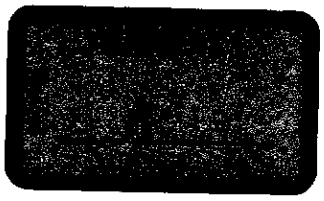
Date of Birth:	October 27, 1956
Marital Status:	Married with two children
Office Address:	Oklahoma City Gynecology and Obstetrics 11200 N. Portland Avenue Oklahoma City, OK 73120 Phone: 405-936-1000
Home Address:	1730 Huntington Avenue Oklahoma City, OK 73116 Phone: 405-858-0955

Education

Bachelor of Arts (German)	Oklahoma State University Stillwater, Oklahoma	1975-1978
Post- Baccalaureate Studies	Oklahoma State University Stillwater, Oklahoma	1980-1986
Doctor of Medicine (with special distinction)	University of Oklahoma College of Medicine Oklahoma City and Tulsa	1987-1991
Residency	Obstetrics and Gynecology University of Oklahoma College of Medicine Oklahoma City, Oklahoma	1991-1995

Awards and Honors

Alpha Omega Alpha
James A. Merrill Award
Resident Teaching Award, University of Oklahoma College of Medicine
Alpha Epsilon Delta Pre-Medicine Honor Society
Phi Kappa Phi Honor Society



Professional Organizations
Fellow, American College of Obstetrics and Gynecology
Oklahoma Section vice chair 2003-2005; Oklahoma Section chair 2005-2008
American Board of Obstetrics and Gynecology, board certified
American Medical Association
Oklahoma State Medical Association-Student member of the Council on State Legislation, 1988-1989
Oklahoma State Medical Association, Council Member on State Legislation 2004 – present; Alternate Delegate to American Medical Association 2007-present
Oklahoma City OB-GYN Society Vice President 2000-2001
Oklahoma City OB-GYN Society President 2001-2002

Organizations and Activities
St. Paul's Episcopal Church, Oklahoma City
P.E.O., chapter president, 1986-1987; chapter vice president, 1985-1986
Kappa Delta Sorority
University of Oklahoma, College of Medicine AIDS Speakers Bureau, 1988
Oklahoma State University Student Government Association 1978-79
Planned Parenthood of Central Oklahoma, board member 2004-present; treasurer 2006-07; vice-president 2007-2008.
Oklahoma Health Center Clinical Pastoral Education Institute, board member 2005-present

Research
Relationship between normal sperm morphology and fertilization in an infertility practice. University of Oklahoma College of Medicine-Tulsa Research Day, 1991

Endometrial thickness as a predictor of pregnancy in clomiphene stimulated cycles. Residents' Research Meeting, Department of Obstetrics and Gynecology, University of Oklahoma College of Medicine, 1993

Human Papillomavirus Types in Cervical Cancer in a University Based Gynecologic Oncology Practice. Residents' Research Meeting, Department of Obstetrics and Gyncecology, University of Oklahoma College of Medicine, 1994

Co-lead investigator, Parke-Davis protocol 376-400421, Mackie site, 1999-2000

Appendix 6

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of its members, ET AL.,	)	
Plaintiffs,	)	Case No. CV-2011-1722
v.	)	
TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health, ET AL.,	)	Judge Daniel L. Owens
Defendants.	)	

DECLARATION OF ABIGAIL A. LONG IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

ABIGAIL A. LONG hereby declares, under penalty of perjury, that the following statements are true and correct:

1. I am the Director of Marketing and Public Affairs for Danco Laboratories, LLC ("Danco"), and I submit this declaration in support of Plaintiffs' Motion for a Temporary Injunction.

2. Danco is the pharmaceutical company that holds the New Drug Application for Mifeprex® (mifepristone) 200mg, oral tablets for medication abortion in the United States. The U.S. Food and Drug Administration ("FDA") approved the New Drug Application, NDA No. 20-687, on September 28, 2000, and Danco has been marketing Mifeprex since then.

3. I am personally familiar with the FDA-approved labeling for Mifeprex, which is called the final printed labeling ("FPL") and consists of four parts: Prescribing Information, Medication Guide, Patient Agreement, and Prescriber's Agreement.

4. Mifeprex is provided in a package that includes a blister pack of tablets and a package insert. The package insert is a document that contains three parts of the FPL: the Prescribing Information, the Medication Guide and the Patient Agreement.

5. A true and accurate copy of the FPL for Mifeprex is attached hereto as "Exhibit A."

6. A true and accurate copy of the Mifeprex package is attached hereto as "Exhibit B."

Executed: January 25, 2012

ABIGAIL A. LONG

Exhibit A

MIFEPREX®

(Mifepristone) Tablets, 200 mg

PRESCRIBING INFORMATION

Contact Information

Danco Laboratories
P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)
www.earlyoptionpill.com

MIFEPREX® (Mifepristone) Tablets, 200 mg
For Oral Administration Only

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following Mifeprex* use. No causal relationship between the use of Mifeprex and misoprostol and these events has been established. Before prescribing Mifeprex, inform the patient about the risk of these serious events and discuss the MEDICATION GUIDE and the PATIENT AGREEMENT. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol.

- Atypical Presentation of Infection. Patients with serious bacterial infections (e.g. Clostridium sordellii) and sepsis can present without fever, bacteremia or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis (see WARNINGS).
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).

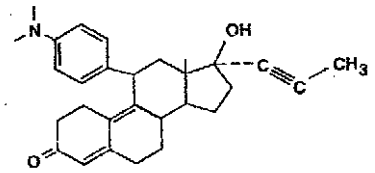
Patients should be advised to take their MEDICATION GUIDE with them if they visit an emergency room or another health care provider who did not prescribe Mifeprex, so that provider will be aware that the patient is undergoing a medical abortion.

* Mifeprex is a registered trademark of Danco Laboratories, LLC.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

CLINICAL PHARMACOLOGY

Pharmacodynamic Activity

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics and Metabolism

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

Clinical Studies

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E_1. All other women without an apparent expulsion took a 400 µg dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the

products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.5% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

Table 1: Outcome Following Treatment with Mifepristone and Misoprostol in the U.S. and French Trials

	U.S. Trials		French Trials	
	N	%	N	%
Complete medical abortion	**762**	**92.1**	**1605**	**95.5**
Timing of expulsion				
Before second visit	52	(6.3)	89	(5.3)
During second visit – less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
– greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
– greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
Surgical intervention	**65**	**7.9**	**76**	**4.5**
Reason for surgery				
Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
Total	**827**	**100**	**1681**	**100**

Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).

INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 µg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) (see WARNINGS);
- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the MEDICATION GUIDE and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review. Patients should discuss their understanding of these materials with their health care providers, and retain the MEDICATION GUIDE for later reference (see PRECAUTIONS).

WARNINGS

Patients must be monitored and undergo appropriate medical evaluation and intervention should any of the following serious adverse events occur following a spontaneous, surgical, or medical abortion, including following Mifeprex use:

1. Vaginal Bleeding

Vaginal bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock (see BOXED WARNINGS). Patients should be counseled to seek immediate medical attention

if they experience prolonged heavy vaginal bleeding following a medical abortion.

According to data from the U.S. and French trials, women should expect to experience vaginal bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of Mifeprex (see BOXED WARNINGS). No causal relationship between these events and the use of Mifeprex and misoprostol has been established. Physicians evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a sustained fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from e.g. *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. Most of these deaths occurred in women who used vaginally administered misoprostol. No causal relationship between Mifeprex and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

3. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of Mifeprex to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion. Medical abortion failures should be managed with surgical termination. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing Mifeprex.

4. Ectopic Pregnancy

Mifeprex is contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies (see CONTRAINDICATIONS). Physicians should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed

ectopic pregnancy since some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex.

PRECAUTIONS

General

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of Mifeprex is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

Information for Patients

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the MEDICATION GUIDE and the PATIENT AGREEMENT. (Additional copies of the MEDICATION GUIDE and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596).

Patients should be advised to review both the MEDICATION GUIDE and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have prior to receiving Mifeprex. Patients should be advised to take their MEDICATION GUIDE with them if they visit an emergency room or another health care provider who did not prescribe Mifeprex, so that provider will be aware that the patient is undergoing a medical abortion.

Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged heavy vaginal bleeding is not proof of a complete abortion;
- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see MEDICATION GUIDE).

Laboratory Tests

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

As of September 2000, over 620,000 women in Europe had taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 received mifepristone together with misoprostol. As of May 2000 a total of 82 cases had been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

Table 2: Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol

	Mifepristone Alone	Mifepristone – Misoprostol	Total
Subsequently had surgical abortion	3	7	10
No abnormalities detected	2	7	9
Abnormalities detected (sirenomelia, cleft palate)	1	0	1
Subsequently resulted in live birth	13	13	26
No abnormalities detected at birth	13	13	26
Abnormalities detected at birth	0	0	0
Other/Unknown	26	20	46
Total	42	40	82

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

Nursing Mothers

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than or equal to 1% in the U.S. and French trials are shown in Table 3.

Vaginal bleeding and uterine cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Vaginal Bleeding). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

Table 3: Type of Reported Adverse Events Following Administration of Mifepristone and Misoprostol in the U.S. and French Trials* (percentages)

	U.S. Trials	French Trials
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Endometritis/Salpingitis/Pelvic Inflammatory Disease	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

*Only adverse reactions with incidence ≥1% are included.

Postmarketing Experience

The following adverse reactions have also been reported during post-approval use of Mifeprex and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. No causal relationship between these events and Mifeprex and misoprostol has been established:

Allergic reaction (including rash, hives, itching), hypotension (including orthostatic), light-headedness, loss of consciousness, post-abortal infection (including endomyometritis, parametritis, pelvic infection), ruptured ectopic pregnancy, shortness of breath, tachycardia (including racing pulse, heart palpitations, heart pounding), and hematometra.

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

DOSAGE AND ADMINISTRATION

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

Day One: Mifeprex Administration

Patients must read the MEDICATION GUIDE and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

Day Three: Misoprostol Administration

The patient returns to the health care provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience vaginal bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4-Early Option (1-877-432-7596)

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Rev 4: 4/22/09

MEDICATION GUIDE

MIFEPREX (MIF-eh-prex) tablets 200 mg
For Oral Administration Only

MIFEPREX® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine, misoprostol, 2 days after you take Mifeprex (Day 3) to end your pregnancy. But about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

Day 1 at your provider's office:

- Read this MEDICATION GUIDE.
- Discuss the benefits and risks of using Mifeprex to end your pregnancy.
- If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
- After getting a physical exam, swallow 3 tablets of Mifeprex.

Day 3 at your provider's office:

- If you are still pregnant, take 2 misoprostol tablets.
- Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.

About Day 14 at your provider's office:

- This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
- Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

■ ■ ■

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09

PATIENT AGREEMENT

Mifeprex® (mifepristone) Tablets

1. I have read the attached Medication Guide for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:

- contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
- contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
- contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol.
- take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.

- return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
- return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05

Contact Information

Danco Laboratories
P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)
www.earlyoptionpill.com

DANCO LABORATORIES

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New York, NY 10185

1.877.4 EARLY OPTION
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MIFEPREX®

(Mifepristone) Tablets, 200 mg

MEDICATION GUIDE

Contact Information

Danco Laboratories
P.O. Box 4816
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MEDICATION GUIDE

MIFEPREX® (Mifepristone) Tablets, 200 mg
For Oral Administration Only

MEDICATION GUIDE

MIFEPREX® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine, misoprostol, 2 days after you take Mifeprex (Day 3) to end your pregnancy. But about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

* Mifeprex is a registered trademark of Danco Laboratories, LLC.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

MIFEPREX® (Mifepristone) Tablets, 200 mg

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

Day 1 at your provider's office:

- Read this MEDICATION GUIDE.
- Discuss the benefits and risks of using Mifeprex to end your pregnancy.
- If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
- After getting a physical exam, swallow 3 tablets of Mifeprex.

Day 3 at your provider's office:

- If you are still pregnant, take 2 misoprostol tablets.
- Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.

About Day 14 at your provider's office:

- This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
- Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

MIFEPREX® (Mifepristone) Tablets, 200 mg

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

■ ■ ■

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09

PATIENT AGREEMENT

Mifeprex® (mifepristone) Tablets

1. I have read the attached Medication Guide for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.

14. I will do the following:

- contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
- contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
- contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol.
- take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
- return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
- return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05

DANCO LABORATORIES

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MIFEPREX® (Mifepristone) Tablets, 200 mg

PATIENT AGREEMENT

Mifeprex* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
    - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
    - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
    - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
    - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
    - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
    - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature:_____ Date:_____

Patient Name (print):_____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature:_____ Date:_____

Name of Provider (print):_____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2:7/19/05

*Mifeprex is a registered trademark of Danco Laboratories, LLC.

MIFEPREX®
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines:

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

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ACCOUNT SETUP FORM

MIFEPREX*(Mifepristone) Tablets, 200 mg; NDC 64875-001-03

To set up your account:

1

Read the Prescriber's Agreement on the back of this Account Setup Form.

2

Complete and sign this form.

3

Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.

4

The distributor will call to finalize your account setup and take your initial order.

5

Subsequent orders may be phoned in and are usually shipped within 24 hours.

6

Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

MIFEPREX*
(Mifepristone) Tablets, 200 mg

Billing information

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Shipping information (❑ Check if same as above)

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name _____ Address _____

City _____ State _____ ZIP _____

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(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials

❑ Medication Guides ❑ Patient Agreements

❑ State Abortion Guidelines ❑ Patient Brochures

Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name _____ Signature _____

Medical License # _____ Date _____

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a registered trademark of Danco Laboratories, LLC.

MAS

Exhibit B

MIFEPREX™ (Mifepristone) Tablets, 200 mg

MIFEPREX™ (Mifepristone) Tablets, 200 mg

RX ONLY NDC 64875-001-05
3 TABLETS (1 DOSE)
Each tablet contains 200 mg Mifepristone. See package enclosure for full prescribing information.
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
Protect from light.

Manufactured for:
Danco Laboratories, LLC
PO Box 4816
New York, NY 10185
1-877-4-EARLY-OPTION
www.earlyoptionpill.com

DANCO LABORATORIES

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Appendix 7

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of its members, ET AL.,	)	
Plaintiffs,	)	Case No. CV-2011-1722
v.	)	
TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health, ET AL.,	)	Judge Daniel L. Owens
Defendants.	)	

DECLARATION OF MARILYN ELDRIDGE IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

MARILYN ELDRIDGE hereby declares, under penalty of perjury, that the following statements are true and correct:

1. I am a co-founder and the President of Nova Health Systems d/b/a Reproductive Services ("Reproductive Services"), one of the Plaintiffs in this action. I provide the following information based on my personal knowledge and the company's books and records.

2. Reproductive Services is a nonprofit corporation whose mission is to provide high-quality and affordable reproductive health care services, including abortion services, to women in underserved communities. Founded in 1973 by a Christian minister, Reproductive Services has operated a total of ten medical clinics in three states. Currently, Reproductive Services operates two medical clinics: one in Tulsa, Oklahoma, and one in El Paso, Texas. The Tulsa clinic has operated continuously since 1974.

3. In 1987, the principals of Reproductive Services founded a nonprofit

organization called Adoption Affiliates, whose mission is to make professional, nonjudgmental adoption services available to women with unintended pregnancies. Reproductive Services and Adoption Affiliates have interlocking boards of directors.

4. Reproductive Services serves women who reside throughout the state of Oklahoma, as well as women who travel from Missouri, Kansas, Arkansas, and Texas to access reproductive health care.

5. There are no licensed abortion providers other than Reproductive Services in the Tulsa, Oklahoma area.

6. Other than Reproductive Services, there are only two health care providers licensed to perform abortions in the State of Oklahoma, both of whom are located at a driving distance of at least two hours from Tulsa, Oklahoma.

7. Reproductive Services is a member of the National Abortion Federation ("NAF"), the largest professional association of abortion practitioners in the United States, and submits itself to inspections by NAF to ensure its compliance with that organization's clinical policy guidelines.

8. Reproductive Services provides medication abortions during the first trimester of pregnancy, up to a gestational age of 8 weeks and 4 days, as calculated from the first day of the woman's last menstrual period ("LMP"). Reproductive Services performs surgical abortions during the first and second trimesters of pregnancy, through a gestational age of 17 weeks LMP.

9. On average, Reproductive Services performs about 200 surgical and medication abortions for our patients each month. In 2010, approximately 90% of the patients seeking abortions at Reproductive Services were in their first trimester.

Approximately 67% of those patients were less than 8 weeks and 4 days pregnant and chose medication abortions.

10. Two physicians provide abortions for women who seek them at Reproductive Services. They are both Board-certified OB/GYNs who work part-time at the clinic.

11. From time to time, women who seek abortions from Reproductive Services have ectopic pregnancies. A patient who is diagnosed with an ectopic pregnancy is sent to Hillcrest Hospital immediately. We send patients to that hospital, rather than the other two area hospitals, because—among other things—we know that Hillcrest can use medication to treat patients with unruptured ectopic pregnancies if the patients are good candidates, whereas the other two hospitals are Catholic and so will only offer surgical treatment for patients with ectopic pregnancies.

12. In the nearly forty years that Reproductive Services has been providing abortions to women, our rate of complications has been extremely low.

13. Every woman seeking an abortion at Reproductive Services first meets with one of our counselors to review and sign a consent form, which includes extensive information about the abortion procedure itself as well as the health and emotional risks involved. At this meeting, the patient is encouraged to ask the counselor questions and discuss any concerns that she may have. In addition, before having an abortion, all of our patients meet with a Reproductive Services nurse to discuss the abortion procedure in detail and to ask any questions. At that meeting, our medication abortion patients are given literature to take home with them that describes in detail the dosage and administration instructions for medication abortion, the potential complications involved

in medication abortion, and what to do in case a medical complication should occur.

14. At Reproductive Services, we offer medication abortion using a combination of the medications mifepristone and misoprostol. The American College of Obstetricians and Gynecologists recommends following an evidence-based regimen for medication abortion rather than the regimen described in the Mifeprex Final Printed Label ("FPL"), and most U.S. abortion providers, including our physicians, use an evidence-based regimen. NAF has also recommended using an evidence-based regimen. In the first stage in the evidence-based regimen our physicians use, a patient receives 200 milligrams of mifepristone at the clinic. She is then instructed to self-administer 800 micrograms of misoprostol within the next six to fourteen hours at a location of her choosing. Our physicians have determined that misoprostol should be administered six to fourteen hours after the patient ingests mifepristone based upon their own experience providing medication abortions and frequent discussions with other abortion providers within Nova Health Systems about the best procedure for medication abortion.

15. Compared with the evidence-based regimen we currently employ, the regimen described in the Mifeprex FPL would subject our patients to greater side effects and a higher risk of health complications. We use the evidence-based regimen because it is safer and more effective for patients than the protocol in the Mifeprex FPL, and we do not want to practice bad medicine.

16. The evidence-based regimen we use has other advantages for patients over the protocol in the Mifeprex FPL and over surgical abortion. In particular, it lets patients have more control over the time and place of the abortion, and it gives them more privacy.

17. In addition, because the FDA regimen calls for the use of three times more mifepristone than the evidence-based regimen currently used at our clinic, it will cost our clinic $156.28 more per patient to administer the FDA regimen. Consequently, Reproductive Services would have to increase the price of medication abortion in order to follow the regimen described in the Mifeprex FPL. Currently, Reproductive Services charges a fee of $550 for either medication or surgical abortion; this fee covers the cost of all medications and follow-up medical appointments. Reproductive Services deliberately set equivalent fees for medical and surgical abortions in order to keep patients from choosing a particular procedure solely based on its cost. I believe that our patients would be discouraged from choosing to have a medication abortion if we were forced to increase the fee for a medication abortion.

18. All of our abortion patients are given written and oral aftercare instructions, including instructions about symptoms to monitor and which symptoms should prompt them to call the clinic. We ask medication abortion patients to call us within a few days to let us know how they are doing, and we reach out to them if we haven't heard from them within a week. In addition, Reproductive Services makes a follow-up appointment for each medication abortion patient approximately 14 days after the administration of mifepristone. If a patient wants to be seen sooner, we will of course see her sooner.

19. At a medication abortion patient's follow-up appointment, she is evaluated to be certain that the abortion is complete and that she is not experiencing any complications. This examination includes a sonogram to confirm that the pregnancy has passed.

20. I have reviewed Oklahoma House Bill 1970 ("the Act"). I do not believe that Reproductive Services would be able to comply with it because I do not understand what it requires us to do. If the Act goes into effect, Reproductive Services will be forced to stop providing medication abortions and may even have to close.

21. Even if the Act were interpreted in a way that would legally permit the use of medication abortions, we might not be able to comply with the Act without harm to our patients, and so we would be forced to stop providing medication abortions entirely. For example, if the Act were interpreted to mean that we could only provide medication abortions according to the protocol described in the Mifeprex FPL, we would probably stop providing medication abortions because our physicians think that the Mifeprex FPL protocol for medication abortions does not meet the standard of care.

22. In addition, if the Act were interpreted to mean that we could only provide medication abortions according to the protocol described in the Mifeprex FPL, we would no longer be able to offer the option of medication abortion to patients who are 49-60 days pregnant, even if a medication abortion would be the best option for them.

23. I believe the Act will cause irreparable injury to Reproductive Services, our staff, and our patients, and that it serves no good purpose.

Executed: January 25, 2012

Marilyn Eldridge /MAN

MARILYN ELDRIDGE

Appendix 8

IN THE DISTRICT COURT OF OKLAHOMA COUNTY
STATE OF OKLAHOMA

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, on behalf of its members, ET AL.,	)	
Plaintiffs,	)	Case No. CV-2011-1722
v.	)	
TERRY L. CLINE, in his official capacity as Oklahoma Commissioner of Health, ET AL.,	)	Judge Daniel L. Owens
Defendants.	)	

DECLARATION OF MARTHA SKEETERS, PH.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

MARTHA SKEETERS, PH.D., hereby declares, under penalty of perjury, that the following statements are true and correct:

1. I am the President and co-Founder of the Oklahoma Coalition for Reproductive Justice ("OCRJ").

2. OCRJ is a membership organization whose mission is to promote reproductive justice in Oklahoma through education and advocacy. Currently, it counts over 300 Oklahoma citizens among its members.

3. OCRJ's members include women of childbearing age who seek to preserve their right to obtain abortion services in Oklahoma without unlawful interference by the government.

4. As the U.S. Supreme Court has recognized, many women, including those who belong to OCRJ, "have organized intimate relationships and made choices that define their views of themselves and their places in society, in reliance on the availability of abortion in the event that contraception should fail." *Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833, 856

(1992) (joint opinion of O'Connor, Kennedy, and Souter, JJ.). "The ability of [these] women to participate equally in the economic and social life of the Nation has been facilitated by their ability to control their reproductive lives." *Id.*

5. It is likely that some members of OCRJ will seek medication abortions or experience ectopic pregnancies in the future.

6. I reside in the State of Oklahoma and pay taxes to the State of Oklahoma. Other members of OCRJ also reside in the State of Oklahoma and pay taxes to the State of Oklahoma.

Executed this 25th day of January, 2012.

Martha Skeeters/MM

MARTHA SKEETERS, PH.D.

Appendix 9

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THE OKLAHOMA STATE CONSTITUTION

A Reference Guide

Danny M. Adkison and
Lisa McNair Palmer

Foreword by W. A. Drew Edmondson

FORDHAM
JUN 28 2001
LAW LIBRARY

REFERENCE GUIDES TO THE STATE CONSTITUTIONS OF THE UNITED STATES, NUMBER 32
G. Alan Tarr, *Series Editor*

GREENWOOD PRESS
Westport, Connecticut • London

called for making many of these positions appointive. They have not had much luck in Oklahoma. In 1975 the voters approved an amendment making the Commissioner of Labor an appointive position, only to amend it back to an elective one in 1988.

Before 1900 it could generally be said of state governments that "the judiciary is the department of our government which has undergone fewest changes and given most satisfaction."[47] Articles in state constitutions covering the judiciary began expanding just prior to the writing of Oklahoma's Constitution. This expansion occurred not only because of distrust of the legislature, but also due to the distrust of judges.[48] The Oklahoma drafters provided for the election of judges to six-year terms. They also followed the lead of other states and staggered the elections of supreme court justices, gave the power of impeachment of judges to the House, gave judges a higher salary than most state officials, specified a jury of less than twelve in select cases, and denied the governor the power to request an advisory opinion from the courts.

REGULATION OF INTERESTS

One area of importance in Oklahoma's Constitution, made obvious by the length devoted to it, is the regulation of certain interests. There are entire articles in the constitution devoted to corporations (Article IX), revenue and taxation (Article X), education (Article XIII), and banks and banking (Article XIV). The articles on corporations and revenue and taxation are each longer than the entire U.S. Constitution. The drafters' distrust of the legislature and other branches is evident in the detail they provided in each of these areas. These details address many of the immediate problems that plagued the state during territorial days. Rather than rely on earlier traditions of state constitutions, the drafters relied on recent state constitutions for designing these articles. There are several explanations for why the drafters thought there was a need to place these lengthy and detailed articles in the constitution.

First, those who had lived in the territories developed a strong dislike for trusts. Between 1897 and 1909, industrial prices rose by 35 percent, and food and fuel costs, critical to the territories' developing economy, jumped 36 and 53 percent respectively.[49] Also, following the publication of Upton Sinclair's *The Jungle*, which vividly portrayed the unsanitary conditions of meat processing plants, a train in Indian Territory had shipped carloads of wheat contaminated with the blood and decay of a decomposed human body.[50] Those living in the territories had also witnessed the railroad industry turning a deaf ear to their complaints to repair a railroad trestle, which finally collapsed and killed nearly 100 Oklahomans.[51] The lesson was that corporations could not be trusted to act in the interest of average citizens. Another factor was taxation. It seemed obvious to anyone who viewed the facts objectively that corporations were not paying their fair share of taxes. "The Atchison, Topeka and Santa Fe Railroad, for example, paid taxes on assessments that averaged less than 8 percent of its

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property's value, whereas individuals in Kiowa County were paying taxes on the basis of 40 percent of market value."[52] Small businessmen, farmers, and laborers felt threatened by this state of affairs. Finally, many people in the territories resented the rise of a wealthy elite; not wealthy per se, but the wealthy that took political steps to see that they prospered at the expense of others, even if it became necessary to engage in corruption.

Had the drafters trusted the legislature to regulate corporations and had they trusted judges to interpret such regulations with the legislators' intentions in mind, they could have left these articles out or at least shortened them a great deal. But, as has already been pointed out, they did not trust the legislators or judges to act in the public's interest. The events occurring during territorial days explain, and perhaps justify, to some degree, their actions. The feeling was expressed by President Murray in his opening address to the delegates: "I know of no interest save the public interest. . . . Let us march forward in solid battalions against the quartette of the railroads, Standard Oil, coal operators, and land grafters whenever they marshal their forces against the people."[53]

The drafters allowed the legislature to pass a variety of taxes:

> The Legislature shall have power to provide for the levy and collection of license, franchise, gross revenue, excise, income, collateral and direct inheritance, legacy, and succession taxes; also graduated income taxes, graduated collateral and direct inheritance taxes, graduated legacy and succession taxes; also stamp, registration, production or other specific taxes. (Article X, Section 12)

Of course, the drafters assumed the state would have the power to tax property. They stipulated that "All property which may be taxed ad valorem ("according to value") shall be assessed for taxation at its fair cash value estimated at the price it would bring at a fair voluntary sale" (Article X, Section 8). To equalize assessments of property taxes among the counties they created a State Board of Equalization (Article X, Section 21). They prohibited the legislature from exempting property from taxation which was not already made exempt by the constitution (Article V, Section 46). They further limited the legislature by stipulating that taxes be uniform and the product of general legislation (Article X, Sections 5 and 14, respectively).

Article X of the constitution, as originally worded, permitted the state legislature to spend more money than was collected in revenue. There were, however, limits on state, county, city, and school district debt. Obviously, given the detail in the Revenue and Taxation Article, the drafters were attempting to tie the hands of a corrupt or controlled legislature. As it turned out, the state experienced years of debt, including the terrible years of the Depression. The deficit was $5 million in 1930 and by 1938 had grown to $26 million.[54] In 1941 the voters approved a constitutional amendment requiring the legislature to balance the budget each year (Article X, Section 23).

Several concerns of labor were addressed in the constitution. The constitution

mandated the creation of a Board of Arbitration and Conciliation (Article VI, Section 21). (Although this section still exists, the Department of Labor, when contacted by the authors, had no knowledge of this Board.)

The drafters also specified:

Eight-hour work days for State, county, or municipal employment (Article XXIII, Section 1).

Convict labor was prohibited (Article XXIII, Section 2).

Employment of children under the age of 15 years was prohibited (Article XXIII, Section 3).

Boys under the age of 18 and women and girls were prohibited from working in mines (Article XXIII, Section 4). (This section was amended in 1986 to apply to boys and girls under the age of 18.)

Eight-hour work days (except for emergencies) for those workers in underground mines (Article XXIII, Section 4).

The legislature is to pass laws protecting the health and safety of employees in factories, mines, and on railroads (Article XXIII, Section 5).

Abrogated, in certain instances, the fellow-servant rule (whereby an employer could reduce his liability for injury to an employee due to the liability of a fellow employee (Article IX, Section 36).

In addition, the Commissioner of Labor's office is a constitutional office (Article VI, Section 20), and since 1915 the state has had a worker's compensation law.

DIRECT DEMOCRACY

Distrust of the legislature found its ultimate expression in the referendum and initiative. Four other states included the initiative and referendum in their constitutions prior to Oklahoma. These devices, in effect, make the people the legislators. Appropriately, they were included in the Legislative Department Article (Article V).

A referendum is a device whereby a bill passed by the legislature is referred to the people for their approval before becoming law. (Amendments, discussed later, are also referred to the voters.) There are two ways in which a referendum may be called. Five percent of the voters or an absolute majority of the legislature may require a referendum vote on a bill passed by the legislature. If a majority voting on the bill votes in favor of it, it becomes law. The voters have generally been disapproving of bills referred to them. They have rejected about 70 percent of the bills the legislature referred to them.

An initiative is a device whereby the people may initiate and pass a bill into law. (Amendments, discussed later, can also be proposed by the initiative.) Eight percent of the voters can propose a bill which will be placed on the ballot; it will become law if approved by a majority of those voting on the bill (prior to

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THE BEST CONSTITUT

William Jennings Bryan
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a 1974 amendment, the "silent vote" operated here). The voters have rejected about 80 percent of the bills proposed through the initiative.

THE BEST CONSTITUTION?

William Jennings Bryan not only called Oklahoma's Constitution the best state constitution, but "a better constitution than the constitution of the United States."[55] Although his characterization was no doubt due to the fact that he was campaigning for ratification, the Oklahoma Constitution did contain many progressive provisions that he advocated: the initiative, the referendum, prohibitions on running for reelection, a progressive income tax, and regulation of corporations, to name a few. Many of these provisions could be found in other state constitutions, but the delegates at Oklahoma's convention brought them all together into one document. One progressive provision conspicuously missing from the document was the recall, probably because Alfalfa Bill Murray said that he never understood its use and therefore opposed it.[56] In advocating certain progressive provisions (such as the initiative and referendum) the delegates may have actually been hindering democracy rather than advancing it. Because so few people bother to take an interest in politics and become knowledgeable about government, these devices "may make possible 'a sort of minority control that is the very antithesis of democracy.' "[57] Rather than write so many policies and regulations into the constitution (creating all the problems that go with lengthy constitutions), the delegates could have concentrated on creating a state government with offices attractive to honest and competent individuals. Murray seemed to understand this. He stated, "Government is only as good as the people running it," and he opposed the recall because he thought it would be a "hindrance to politicians exercising courage."[58]

Probably the criticism most often aimed at Oklahoma's Constitution is its length. What problems are associated with lengthy constitutions?

LENGTHY CONSTITUTIONS

If a constitution sought to "contain an accurate detail of all the subdivisions of which its great powers will admit, and of all the means by which they may be carried into execution," Chief Justice John Marshall observed in 1819, it "would partake of the prolixity of a legal code."[59] Such a constitution, he suggested, "would probably never be understood by the public." Yet in 1907 the drafters of Oklahoma's Constitution ignored Marshall's advice and created a "legal-code" type of constitution. As originally drafted, it contained approximately 50,000 words. It was ten times as long as the unamended U.S. Constitution, and over three times as long as all other state constitutions up to 1907.

The primary explanation for why the drafters of Oklahoma's Constitution opted for a long constitution was the lack of trust in legislatures. One funda-