IN THE SUPREME COURT OF THE STATE OF OKLAHOMA

TERRY CLINE, et al.,	)	
	)	
Petitioners,	)	
	)	
vs.	)	No. 111,939
	)	
OKLAHOMA COALTION FOR REPRODUCTIVE JUSTICE,	)	
	)	
Respondents.	)	

AMICUS CURIAE BRIEF OF DR. MARY MARTIN, M.D., FACOG; DR. RITA SANDERS, D.O., FACOG; DR. PABLO PINZON, M.D., FACOG; AND DR. MICHAEL GLASS, M.D., FACOG, IN SUPPORT OF THE PETITIONERS

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SUBJECT INDEX WITH AUTHORITIES

Other Authorities

STATEMENT OF INTEREST OF *AMICI CURIAE*

Amici Curiae consist of Dr. Mary Martin, M.D., FACOG; Dr. Rita Sanders, D.O, FACOG; Dr. Pablo Pinzon, M.D., FACOG; and Dr. Michael Glass, M.D., FACOG. All are Oklahoma Doctors, each of whom is duly licensed to practice medicine in Oklahoma and currently specializes in the practice of obstetrics and gynecology in Oklahoma.

For the reasons set forth in this brief, it is the medical opinion of *Amici* that H.B. No. 1970, Section 1, Chapter 216, O.S.L. 2011 (the "Act") properly reflects sound medical evidence which demonstrates that the FDA-approved Mifeprex Regimen, including the use of misoprostol as prescribed in the FDA-approved protocol, is safer than off-label uses of mifepristone and/or misoprostol to induce a medical abortion. Since surgical abortion is always available and is safer and faster than medical abortion, the State's restriction of medical abortions from 63 to 49 days poses no undue burden on access to abortion. Further, since treatment of ectopic pregnancy and medical abortion are considered separate procedures by the medical community, the Act's restrictions on medical abortions in no way restrict the use of methotrexate to treat ectopic pregnancies.

The interest of *Amici* is to ensure that the women entrusted to their care receive accurate, objective information about the health risks of any intervention provided, and that patient well-being and safety are protected. *Amici* take further interest in this case since they are among the doctors responsible for treating the resultant injuries to women that arise when the FDA protocol is not followed. *Amici* believe their expertise on the medical issues related to the use of Mifeprex that are implicated in this case will assist the Court in understanding the rationality of the State of Oklahoma's legislative decision to require, as a matter of health and safety, that the Mifeprex Regimen be administered as labeled by the FDA.

ARGUMENT

The Act, codified at 63 Oklahoma Statute § 1-729a (2012), is a medical regulation, enacted to protect women's health, which requires that the Mifeprex Regimen be administered consistently with the protocol approved by the FDA. As discussed below, off-label use of the Mifeprex Regimen poses significant health risks for women. The regulation is rationally related to the protection of a pregnant woman's health and neither bans the use of misoprostol nor restricts the use of methotrexate in the treatment of an ectopic pregnancy. Thus, the challenged statute does not on its face impose a substantially "undue burden" on a woman's access to abortion.

PROPOSITION 1:

CONSISTENT WITH MISOPROSTOL'S DRUG LABEL AND THE FDA'S APPROVED REGIMEN, MISOPROSTOL MAY BE USED (IN CONJUNCTION WITH MIFEPRISTONE) TO INDUCE AN ABORTION UP TO AND INCLUDING 49 DAYS GESTATION.

The Act allows for use of misoprostol in conjunction with mifepristone to induce abortions consistent with the FDA-approved protocol up to and including 49 days gestation. Any use of misoprostol to induce an abortion in a manner not specified in the Final Printed Label ("FDA Label") for mifepristone is considered an "off-label" use and is thus prohibited by the Act. This prohibition would include use of mifepristone and misoprostol at gestational ages greater than 49 days, or at dosages other than those specified in the FDA Label for mifepristone.

Mifeprex is a two-drug regimen of mifepristone and misoprostol, which, when effective, induces an abortion. Under the protocol approved by the FDA, a woman takes the first drug (mifepristone) at a doctor's office or abortion clinic. Mifepristone blocks progesterone, a hormone necessary for the uterus to provide nourishment for the embryo and

fetus. Progesterone blockade causes the maternal side of the placenta to disintegrate, effectively starving the unborn child.[1] But, mifepristone used alone will cause the uterus to expel the dead embryo or fetus in only half of the time. Although some studies using mifepristone alone have ultimately produced completion rates as high as 60–80%, it is widely recognized that, by itself, mifepristone is not a viable substitute for surgical abortion.[2] Thus, a second drug, misoprostol (a prostaglandin which induces contractions to expel the embryo and placental tissue), is administered 36 to 48 hours later to cause uterine contractions. Independently, neither mifepristone nor misoprostol is FDA-approved for abortions. To date, the Mifeprex Regimen of both mifepristone and misoprostol is the only FDA-approved regimen for medical abortion.[3]

A. MIFEPREX REGIMEN: THE FINAL PRINTED LABEL

The Act defines "drug label" as

> 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

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[1] I.M. Spitz, *Mifepristone: Where Do We Come From and Where Are We Going? Clinical Development over a Quarter of a Century*, 82 CONTRACEPTION 442, 443 (2010) ("If implantation has occurred, the inhibition of transcription by the mifepristone-PR complex results in down-regulation of progesterone-dependent genes with decidual necrosis and detachment of products of conception. Mifepristone also acts on endometrial blood vessels, causing vascular damage that further compromises the embryo. It also directly promotes uterine contractions.").

[2] *See* Citizen Petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days Gestation, *at* Note 87, *available at* http://www.fda.gov/ohrms/dockets/dailys/02/Aug02/082002/02p-0377-cp00001-01-vol1.pdf; M.D. CREININ, NAT'L ABORTION FEDERATION, EARLY MEDICAL ABORTION WITH MIFEPRISTONE OR METHOTREXATE: OVERVIEW 4 (2002) (reporting that "for gestations up to 49 days, complete abortion occurs in approximately 60% to 80%" of women using mifepristone alone). *See also* H. von Hertzen, *Research on Regimens for Early Medical Abortion*, 55 JAMA 133 (2000).

[3] FOOD & DRUG ADMIN., *Final Printed Label: Mifeprex (mifepristone) Tablets*, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm (last visited Aug. 9, 2013).

> 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.[4]

The label for RU-486 reflects the FDA's approved protocol and lays out clearly the responsibilities of the patient and physician:

> 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.[5]

The FDA Label calls for a series of three visits.[6] On Day One, the FDA Label calls for administration of Mifeprex in a single oral dose of three 200 mg tablets (600 mg) of

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[4] OKLA. STAT. tit. 63, § 1-729(a).

[5] FOOD & DRUG ADMIN., *Mifeprex Final Printed Label*, *supra* note 3.

[6] The label states:

> 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 healthcare 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.

Mifeprex.[7] On Day Three, two days after ingesting Mifeprex, the Patient is instructed to return to her healthcare provider. "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."[8] Additionally, Patients are instructed to "return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to

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> 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 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 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).

Id.

[7] *Id.*

[8] *Id.*

confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred."[9]

These three patient visits were determined to be essential to patient safety. The American College of Obstetricians and Gynecologists ("ACOG") has stated: "Medical abortion should be considered a medically acceptable alternative to surgical abortion in selected, carefully counseled and informed women."[10] The implication of this statement is that of all women who present with a desire for early abortion, only a subset of those women may safely qualify for medical abortion. In discussing what factors determine whether a woman is a candidate for a medical abortion, ACOG states:

> Although medical contraindications are infrequent, social or psychological 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 (e.g. surgical curettage for hemorrhage). Counseling should include a description of cramping and bleeding and should indicate that, rarely the process may not be completed in several weeks.[11]

Thus, medical abortion is indicated for a subset of women who desire abortion and who are willing to commit to the process of medical abortion which "requires follow-up to ensure completion of the abortion"[12] and requires "patient participation throughout a multiple-step

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[9] *Id.*

[10] Am. Coll. of Obstetricians & Gynecologists, *Medical Management of Abortion*, ACOG PRACTICE BULLETIN No. 67 (Oct. 2005) [hereinafter ACOG Practice Bulletin 67].

[11] *Id.*

[12] Table 2: Features of Medical and Surgical Abortion, *in* ACOG Practice Bulletin 67.

process."[13] This requirement of "follow-up to ensure completion" and "participation throughout a multiple-step process" holds true regardless of the method of administration of medical abortion and regardless of the dosages of mifepristone and misoprostol employed.

B. THE FDA-APPROVED PROTOCOL BEST PROTECTS WOMEN'S HEALTH AND SAFETY.

The FDA protocol differs from off-label regimens in three important ways. First, the FDA-approved protocol limits its use to 49 days gestation. Secondly, the FDA-approved protocol uses different dosages and methods of administration of the drugs given than the off-label uses. Thirdly, the FDA-approved protocol requires that the patient be seen and evaluated for completion of the abortion before being given the misoprostol in order to minimize women's exposure to unnecessary drugs. Importantly, the issue of limitation on gestational age for medical methods, the doses of medications employed and the method of administration of mifepristone and misoprostol properly revolves around the concern for safety for woman, as opposed to convenience for the abortion provider.

1. Since the Risk of Hemorrhage, Retained Tissue, and Ongoing Pregnancy Increase with All Regimens After 49 Days Gestation, the FDA-Approved Protocol Limits Medical Abortion to 49 Days Gestation out of Concern for the Health and Safety of Women. Surgical Abortion, Which Is Safer Than Medical Abortion at All Gestational Ages, Is Available for Women Who Do Not Qualify for Medical Abortion.

At the time they approved the Mifeprex Regimen, the FDA was aware of alternative protocols, including different timing and administration of mifepristone and misoprostol and extension of use beyond 49 days. Of note is the fact that at 49 days gestation or less, the

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[13] *Id.*

FDA-approved protocol has the same efficacy as any off-label protocol.[14] In the interest of the safety of women, the FDA limited use of the medical abortion regimen to 49 days gestation or less. That is because the incidence of complications with medical abortion increases after 49 days gestation, regardless of the protocol used.

Medical research documents that medical abortions decline in efficacy and safety after 49 days gestation, thus supporting the FDA's decision to limit use of the Mifeprex Regimen to 49 days or less, and the State of Oklahoma's decision to adopt that guideline. Regardless, restrictions on medical abortion do not in any way affect the availability of surgical abortion throughout the first trimester. Surgical abortion is available throughout the first trimester. It is quicker and has fewer side effects than medical abortion. Thus, the State's ban on off-label medical abortions in no way bars access to abortion, since a quicker, simpler alternative (surgical abortion) exists, with fewer failures and complications.[15]

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[14] *See* ACOG Practice Bulletin 67, *supra* note 10; R. Kulier et al., *Medical Methods for First Trimester Abortion*, COCHRANE DATABASE SYST. REV. Issue 11. Art. No.: CD002855 (2007); B. Winikoff et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Controlled Trial*, 112 OBSTET. GYNECOL. 1303, 1303 (2008).

[15] *See* J. Jensen et al., *Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study*, 59 CONTRACEPTION 153 (1999); M. Niinimaki et al., *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy*, 114 OBSTET. GYNECOL. 795 (2009); C. Rorbye et al., *Medical Versus Surgical Abortion Efficacy, Complications and Leave of Absence Compared in a Partly Randomized Study*, 70 CONTRACEPTION 393 (2004). *See also* R.C. Henshaw et al., *A Comparison of Medical Abortion (Using Mifepristone and Gemeprost) with Surgical Vacuum Aspiration: Efficacy and Early Medical Sequelae*, 9 HUMAN REPRO. 2167, 2167 (1994) ("Results were gestation-related; at <50 days of amenorrhoea there was little to choose between the two procedures. At 50-63 days of amenorrhoea medical abortion becomes more painful and less effective, whereas vacuum aspiration retains high tolerance and efficacy. Women who are unsure which method to use are likely to find vacuum aspiration more acceptable at longer gestations.").

At gestational ages over 49 days, the complications from medical abortion increase regardless of the regimen used.[16] Recently, one study looked at the rates of the most common complications of medical abortion performed primarily using mifepristone and vaginal misoprostol, which constitute the most common off-label use in the United States. The study found an increased rate of both surgical re-evacuation and infection in medical abortions with off-label mifepristone/misoprostol regimens.[17]

It was because of the increase in complications after 49 days for all regimens of medical abortion that the FDA limited use of the Mifeprex Regimen to 49 days or less. Though the FDA was aware at the time of alternative regimens beyond 49 days, it deliberately chose to limit the use of the Mifeprex Regimen to 49 days or less due to concerns about patient safety and effectiveness of the regimens. Regardless of the regimen used, the side effects of medical abortion, including ongoing pregnancies and retained tissue increase beyond 49 days.

Medical researchers Ngoc and Winnikoff analyzed the success rates of the off-label regimen of mifepristone and buccal misoprostol at gestational ages greater than 49 days as compared with 49 days. They found that the completed abortion rate at 49 days was 97.5% as compared to the completed abortion rate at 50-56 days, which dropped to 89.3%. Similarly, the ongoing pregnancy rate at 49 days or less was 0.6% versus an ongoing

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[16] *See* E.G. Raymond et al., *First-Trimester Medical Abortion with Mifepristone 200 mg and Misoprostol: A Systematic Review*, 87 CONTRACEPTION 26 (2012).

[17] M.J. Mentula et al., *Immediate Adverse Events after Second Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study*, HUMAN REPRO. 1 (2011).

pregnancy rate of 7.1% at 50-56 days gestation. And finally, the rate of need for surgery for failure abortions was 1.9% at 49 days or less compared with 3.6% at 50-56 days gestation.[18]

Surgical abortion, while not without its own risks, is safer than medical abortion. Research conducted by M. Niinimaki identified complications within 42 days after either medical or surgical abortion using "high-quality registry data" obtained from 42,619 women in Finland who underwent abortions using mifepristone with vaginal or sublingual misoprostol from 2000-2006 with a gestational duration of ≤63 days. The study found: the incidence of hemorrhage was 15.6 percent following medical abortions, compared to 5.6 percent for surgical abortions; 6.7 percent of medical abortions result in incomplete abortion, compared to 1.6 percent of surgical abortions; and the rate of need for surgery following medical abortion was 5.9 percent.[19]

Other studies confirm the findings of the Niinimaki study, and comment on the high incidence of pain and side effects in Mifeprex abortion patients versus surgical abortion patients. Mifeprex patients report "significantly longer bleeding" and "significantly higher levels" of pain, nausea, vomiting, and diarrhea than women who have surgical abortions.[20] A 2011 study found that 5.7% of women using Mifeprex required readmittance to a hospital while only 0.4 percent of patients required readmittance after surgical abortion.[21] Other research has shown similar results (failure rates for medical abortion (5.2–16.0%) exceeded

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[18] N.T.N. Ngoc et al., *Comparing Two Early Medical Abortion Regimens: Mifepristone+Misoprostol vs. Misoprostol Alone*, 83 CONTRACEPTION 410, 415 (2010).

[19] Niinimaki, *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy*, *supra* note 15, at 799.

[20] Jensen, *supra* note 15, *at* 156 (finding that a higher percentage of RU-486 patients experienced failure (18.3%) than those who had surgical abortions (4.7%)).

[21] E. Mulligan & H. Messenger, *Mifepristone in South Australia: The First 1343 Tablets*, 40 AUST. FAMILY PHYSICIAN 342, 343 (2011).

those of surgical abortion (0–4.0%).[22] "Women receiving mifepristone/misoprostol are more likely to require an unplanned surgical intervention than women who undergo suction curettage. They experience more discomfort with their procedure and in the follow-up interval, bleed for a longer period, and remain at risk for surgical completion curettage for several weeks."[23] Studies have also found that complications of medical abortion were severe enough that between 13–15% of women obtaining them consulted their general practitioner afterwards.[24] In addition, recent studies in mice raise concern about the effects of mifepristone abortions on the outcomes of subsequent pregnancies.[25] And a 2013 study in humans demonstrated an increased risk of growth-restricted infants in pregnancies which take place less than six months after medical abortion.[26]

In short, limiting of the option of medical abortion to gestations less than 49 days was a determination made by the FDA in consideration of patient safety and the availability of a quicker, less risky procedure (surgical abortion) at gestations after 49 days. Since surgical abortion is legal, and must be available 24/7[27] on an emergency basis in every situation

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[22] B. Winikoff et al., *Safety, Efficacy, and Acceptability of Medical Abortion in China, Cuba, and India: A Comparative Trial of Mifepristone and Misoprostol Versus Surgical Abortion*, 176 AM. J. OBSTET. GYNECOL. 431 (1997).

[23] Jensen, *Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study*, *supra* note 15, *at* 153.

[24] H. Hamoda et al., *A Randomized Controlled Trial of Mifepristone in Combination with Misoprostol Administered Sublingually or Vaginally for Medical Abortion Up to 13 Weeks of Gestation*, 112 BJOG 1106, 1106 (2005).

[25] F. Lv et al., *Repeated Abortion Affects Subsequent Pregnancy Outcomes in BALB/c Mice*, 7 PLOS ONE 1 (2012).

[26] X.X. Huo et al., *Effect of Interpregnancy Interval after a Mifepristone-Induced Abortion on Neonatal Outcomes in Subsequent Pregnancy*, 87 CONTRACEPTION 38 (2013).

[27] As per the requirements of:

where medical abortion is used, it is incoherent to argue that limitation of medical abortion to 49 days gestation or less constitutes an "undue burden" on women. Medical abortion is an additional option for certain women carefully selected based on safety concerns, but surgical abortion is the less risky standard.

2. Off-Label Protocols Call for Higher Dosages and Different Means of Administration of Misoprostol, Which Have Been Linked to Infection and Death.

The FDA-approved regimen requires 600 mg of mifepristone. The off-label protocols require 200 mg of mifepristone. However, in order for the off-label protocols to compensate for the lowered dosage of mifepristone, the dosage of misoprostol has to be doubled. The FDA protocol uses 400 μg of misoprostol administered orally. The off-label protocols use double that dose (800 μg) administered vaginally, buccally, or sublingually. Oral misoprostol remains in the body for a much shorter time than vaginal, buccal, or sublingual administration of misoprostol, because of the way in which oral doses are metabolized.[28] So, in addition to doubling the dose, the off-label protocols expose a woman to more than double the amount of the drug's effect, for a longer duration than the FDA protocol. This longer

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1) The National Abortion Federation's Clinical Guidelines: "Standard 6: The patient must be informed that a surgical abortion will be recommended if medical abortion fails and this must be documented. Standard 7: The facility must provide an emergency contact service on a 24-hour basis and must offer or assure referral for uterine aspiration if indicated." NAT'L ABORTION FED., CLINICAL POLICY GUIDELINES 13 (2012).
2) The American College of Obstetricians and Gynecologists: "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 should be trained in surgical abortion or should work in conjunction with a clinician who is trained in surgical abortion." ACOG Practice Bulletin 67, *supra* note 10, *at* 6.

[28] *See* K.G. Danielsson et al., *Comparison Between Oral and Vaginal Administration of Misoprostol on Uterine Contractility*, 93 OBSTET. GYNECOL. 275 (1999); E.A. Schaff, *Mifepristone Review 10 Years Later*, 81 CONTRACEPTION 1 (2010); M. Zieman, *Absorption Kinetics of Misoprostol with Oral or Vaginal Administration*, 90 OBSTET. GYNECOL. 88 (1997).

exposure is necessary to compensate for the lesser amount of mifepristone given in the off-label protocols.[29]

But, misoprostol administration in pregnancy carries significant risks, especially at gestational ages beyond the FDA limit of 49 days (seven weeks). The misoprostol label carries this "black box" warning:

> CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY.[30]

The FDA approved regimen calls for a significantly lower dose of misoprostol than off-label protocols. This is relevant to health and safety concerns because it is the dose and route of administration of misoprostol which is most implicated in the massive fatal infections seen after some medical abortions.[31] The FDA discovered that women who died of overwhelming infections after medical abortions all took 800 μg of misoprostol by vagina or buccal route instead of the FDA approved oral route of administration.[32] In addition, fatal

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[29] *See* B. Winikoff et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Controlled Trial*, *supra* note 14.

[30] FOOD & DRUG ADMIN., *Final Printed Label: Cytotec (misoprostol)*, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19268slr037.pdf (last visited Aug. 12, 2013).

[31] *See* D.M. Aronoff et al., *Misoprostol Impairs Female Reproductive Tract Immunity Against Clostridium Sordelli*, 180 J. IMMUNOL. 8222 (2008); Spitz, *supra* note 1, at 444 ("It has been shown in rats that intrauterine misoprostol increases mortality from *C. sordellii* infection by impairing the immune response.").

[32] A.L. Cohen et al., *Toxic Shock Associated With Clostridium sordellii and Clostridium perfringens After Medical and Spontaneous Abortion*, 110 OBSTET. GYNECOL. 1027 (2007); D. Soper, *Abortion and Clostridial Toxic Shock Syndrome*, 110 OBSTET. GYNECOL. 970 (2007).

sepsis has been seen after use of vaginal misoprostol alone, without mifepristone.[33] A recent review article states:

> Since 1977, there are 12 reported cases of death from infections associated with *C. sordellii* or *C. perfringens* after induced abortion. One case involved therapeutic induction of labor at 19 weeks using laminaria followed by 3 doses of vaginal misoprostol 400 mcg. Testing revealed *C. perfringens* in uterine and placental tissues. A second case occurred after surgical abortion at 12 weeks. In this case, minimal clinical information was recorded but PCR testing of endometrial tissue was positive for *C. perfringens*. All remaining cases followed medical abortion with mifepristone 200 mg orally and misoprostol 800 μg (vaginal=9, buccal=1). One case demonstrated *C. perfringens* in the uterine and cervicovaginal tissues, whereas the remaining 9 deaths were attributed to *C. sordellii*. The ages of affected women range from 16 to 34 years and the gestational ages at which their medical abortions were initiated range from 5 to 10 weeks.[34]

In contrast, there have been no deaths from the FDA protocol.[35]

Misoprostol is itself indicated as a cause of the massive infections seen with off-label use,[36] and the increased 800 microgram dose of misoprostol is associated with deaths from *C.*

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[33] *See* Cohen, *Toxic Shock Associated With Clostridium sordellii and Clostridium perfringens After Medical and Spontaneous Abortion*, *supra* note 32; Soper, *Abortion and Clostridial Toxic Shock Syndrome*, *supra* note 32, *at* 970 ("Additionally, the authors present two cases of postabortion sepsis associated with *Clostridium perfringens*. One case (Patient 1), associated with an intravaginal misoprostol-induced second-trimester abortion, has all the characteristics of the classic, fulminant, necrotizing clostridial infection associated with intravascular hemolysis most reported before the legalization of abortion in 1965.").

[34] A. Dempsey, *Serious Infection Associated With Induced Abortion in the United States*, 55 CLINICAL OBST. & GYNECOL. 888, 889 (2012).

[35] FOOD & DRUG ADMIN., MIFEPRISTONE U.S. POSTMARKETING ADVERSE EVENTS SUMMARY THROUGH 04/30/2011, RCM 2007-525, *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf [hereinafter FDA Fact Sheet].

[36] *See* Dempsey, *Serious Infection Associated with Induced Abortion in the United States*, *supra* note 34, *at* 890 ("Impaired immunity caused by either or both medications has also been proposed as a potential mechanism. Theoretically the progesterone and glucocorticoid antagonism of mifepristone may lead to altered release of cytokines and cortisol which in turn may impair innate immunity. In

sordellii sepsis, whether vaginally or buccally administered. One study which reviewed the initial deaths after medical abortion stated:

> The combination oral regimen of the progesterone/glucocorticoid receptor antagonist mifepristone (also known as RU-486) and the PGE1 analog misoprostol received approval by the U.S. Food and Drug Administration in September 2000 for use in the termination of pregnancy of 49 days duration. Soon after, there were five reported cases of otherwise healthy women who developed (and died from) an acute "toxic shock" syndrome complicating *Clostridium sordellii* endometritis within days of undergoing medical abortion with these agents (1, 2). These five cases were associated with the off-label administration of an increased dose of misoprostol (800 μg in lieu of the approved 400 μg) applied directly into the vagina, as opposed to the approved oral use. More recently, an additional three cases of medical abortion-associated clostridial endometritis have been reported (3), with two cases involving the intravaginal administration of Misoprostol.[37]

There have also been reports of massive lethal infections from the use of misoprostol alone, without mifepristone.[38]

Exposing women to a higher dose of misoprostol is a safety concern. There have been zero reported deaths from *C. Sordellii* using the 400 microgram oral dose of misoprostol. Vaginal, buccal, and sublingual misoprostol administration results in much greater concentrations in a woman's body for a longer period of time than does the oral route

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addition, there is some evidence to suggest that high local levels of misoprostol, a PGE2 analog, in uterine tissue of rats may impair innate immunity to clear *C. sordellii*.").

[37] Aronoff, *Misoprostol Impairs Female Reproductive Tract Immunity against Clostridium Sordelli*, *supra* note 31, *at* 8222–23.

[38] *See* Cohen, *Toxic Shock Associated With Clostridium sordellii and Clostridium perfringens After Medical and Spontaneous Abortion*, *supra* note 32; Soper, *Abortion and Clostridial Toxic Shock Syndrome*, *supra* note 32.

of misoprostol administrations.[39] This greater concentration of drug for prolonged time periods explains the increased risks of infection associated with off-label use of misoprostol which are not associated with the FDA protocol.

Planned Parenthood, in recognition of the concern and danger from higher misoprostol doses has itself ceased off-label vaginal misoprostol use.[40] Instead, they are now experimenting with high dose buccal/sublingual misoprostol. However, the FDA has also reported a death from 800 μg of buccally administered misoprostol.[41] In 2010, the CDC published comments on Planned Parenthood's decision to cease off-label vaginal administration of misoprostol:

> As previously reported in the Journal, Planned Parenthood Federation of America health centers changed their recommended regimen for medical abortions in the years 2006 and 2007, administering buccal rather than vaginal misoprostol and adding routine prophylactic antibiotics (doxycycline) in response to rare reports of serious infection after medical abortion. The effectiveness of this revised regimen in preventing *C. Sordellii* infections and the safety of routine administration of antibiotics for this procedure remain unknown.[42]

So, far from extolling the safety of the buccal administration of misoprostol CDC researchers in 2010 state instead that the effectiveness and safety of this change in protocol is "unknown." In light of the "unknown" safety and efficacy of the off label regimens, it is

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[39] *See* Danielsson, *supra* note 28; Schaff, *supra* note 28; Zieman, *supra* note 28.

[40] *See* M. Fjerstad et al., *Severity of Infection Following the Introduction of New Infection Control Measures for Medical Abortion*, 83 CONTRACEPTION 330 (2011). *See also* Gardiner Harris, *Some Doctors Voice Worry over Abortion Pills' Safety*, N.Y. Times, April 1, 2006, at A11; Gardiner Harris, *After 2 More Deaths, Planned Parenthood Alters Method for Abortion Pill*, N.Y. Times, March 18, 2006, at A10.

[41] *See* Schaff, *Mifepristone Review 10 Years Later*, *supra* note 28.

[42] E. Meites et al., *Fatal Clostridium Sordellii Infections after Medical Abortions*, 363 N. ENG. J. MED. 1382 (2010).

reasonable for the State of Oklahoma to limit the provision of abortion to the FDA regimen, which has an equivalent effectiveness for pregnancies at 49 days or less, and has never been associated with deaths from overwhelming sepsis.

3. The FDA-Approved Protocol's Requirement That the Patient Be Seen and Evaluated for Completion of the Abortion Before Being Given the Misoprostol Minimizes Exposure to Unnecessary Drugs and Protects Women's Health and Safety.

Finally, the FDA regimen differs from off-label protocols in that it requires a second visit before administering the misoprostol to see whether or not the woman has completed the abortion with mifepristone alone[43] (and 2–3% percent will complete with mifepristone alone within two days of ingestion),[44] and whether or not the woman actually even needs the misoprostol at all. If administration of mifepristone alone causes a complete abortion, then the woman does not need to take misoprostol, sparing her from any potential side effects caused by the misoprostol. If her abortion is documented as complete, she also needs no further follow-up exam. In the case of these women, the second visit prescribed by the FDA-approved protocol is an integral and necessary component to protect women's health and to keep these women from unnecessary exposure to a potent drug known to be associated with fatal infections.

If the pregnancy is documented not to be complete, then misoprostol is ingested at the second visit. The World Health Organization's 2003 Technical Guidance on safe abortion states: "Following administration of the prostaglandin at the second visit, the standard observation period is 4-6 hours, during which up to 90% of women will expel the products of

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[43] FDA Fact Sheet, *supra* note 35.

[44] H. Azem El-Refaey, *Induction of Abortion with Mifepristone (RU-486) and Oral or Vaginal Misoprostol*, 332 N. ENG. J. MED. 983, 984 (1995).

conception."[45] Subsequent studies confirm similar rates of rapid completion of pregnancy termination.[46] Thus this second visit also allows an opportunity for the clinic to supervise the woman during the most difficult and painful part of the expulsion, and to provide adequate pain management and support during that most difficult time of expulsion. This four-hour observation period is not explicitly required by the FDA protocol, but it is implied by the ACOG Practice Bulletin 67.[47]

Documentation of completion of the abortion at this second visit allows these women, under the FDA protocol, to avoid a third visit in two weeks to document completion of the abortion. If completion of the pregnancy termination is documented at this second visit, either before or subsequent to misoprostol ingestion, then there is no need for a third visit to confirm completion of the pregnancy termination, since completion will have been documented at this second visit.

The third visit in the FDA protocol pertains only to those 10% of women who have not been documented to have completed the termination of pregnancy at the end of the second visit, if the observation period which is implied in the ACOG practice bulletin has been observed. It is that subset of 10% of women for whom it is essential that a third visit take place to document completion of the termination, as misoprostol is a known teratogen[48]

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[45] WORLD HEALTH ORG., SAFE ABORTION: TECHNICAL AND POLICY GUIDANCE FOR HEALTH SYSTEMS 37 (2003).

[46] *See e.g.,* El-Refaey, *Induction of Abortion with Mifepristone (RU-486) and Oral or Vaginal Misoprostol, supra* note 44; R. Peyron et al., *Early Termination of Pregnancy with Mifepristone (RU 486) and the Orally Active Prostaglandin Misoprostol*, 328 N. ENG. J. MED. 1509 (1993).

[47] ACOG Practice Bulletin 67, *supra* note 10, at Table 1: Advantages and Disadvantages.

[48] *See* P. Barbero, *Misoprostol Teratogenicity: A Prospective Study in Argentina*, 109 ARCH. ARGENT. PEDIAT. 226 (2011); S. Mengue et al., *Misoprostol, Abortion, and Congenital Malformations*, 30 REV. BRAS. GINECOL. OBSTET. (Rio de Janeiro, 2008).

and can cause significant deformities in fetuses exposed to the drug.[49] In addition to the teratogenic exposure of ongoing pregnancies, other complications such as retained tissue must be assessed at this third visit, in order to assure that the termination has been completed and that the woman's health and safety are preserved.

All of these visits are focused on patient safety issues, for the purpose of providing important information to the patient and abortion provider, and minimizing the exposure to unnecessary doses of drugs which can have significant side effects.

The ACOG practice bulletin states that medical abortion is for carefully screened women who are capable of returning for follow-up visits. If a woman is not capable of returning for follow-up visits, then she is not a candidate for medical abortion, and should have instead a surgical abortion, which is quicker and can be completed in a single visit.

It is better for the woman to not take a drug like misoprostol, whose method of administration has been linked to overwhelming sepsis and death, unless it is needed. However, the alternative, non-FDA approved, regimens instruct the woman to take 800 μg of misoprostol at home whether or not she has expelled the pregnancy and whether or not she actually needs to be exposed to that drug. It is obvious that such alternative regimens provide substantial advantage to the abortion provider, who does not have to be available or responsible for a second visit, but it is clearly not in the best interests of the patient, who may be needlessly exposed to double the dose of misoprostol [800 micrograms in the off-label protocol instead of 400 micrograms in the FDA protocol], a drug known to have potential

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[49] *See* FOOD & DRUG ADMIN., *Final Printed Label: Cytotec (misoprostol)*, *supra* note 30. *See also* C.H. Gonzales et al., *Congenital Abnormalities in Brazilian Children Associated with Misoprostol Misuse in First Trimester Pregnancy*, 351 LANCET 1624 (1998); E.S. Opaleye et al., *Evaluation of the Teratogenic Risks in Gestations Exposed to Misoprostol*, 32 REV. BRAS. GINECOL. OBSTET. 19 (2010).

negative side-effects when administered vaginally, buccally, or sublingually. It is these 800 μg doses of misoprostol which have been linked to the deaths of women from sepsis.[50]

Unlike the FDA protocol, which is clear and explicit, the appeal to "alternative regimens" (i.e., off-label protocols) is nebulous. The "alternative regimen" mentioned in the ACOG practice bulletin (800 μg of misoprostol administered vaginally) is not even used now because of the concerns over fatal infections. And the "alternative regimen" of buccal and sublingual dosing which is still in the experimental phases, has already been linked to one US death. In addition, until 49 days gestation, there is no difference in effectiveness between the alternative regimens and the FDA regimen.[51] Thus, at 49 days or less, the primary consideration must be patient safety.

The reason that the FDA exists is to provide an objective scientific analysis of the safety and efficacy of a drug regimen. The manufacturers of mifepristone are free at any time to submit a new drug application and prove the safety and efficacy of a proposed regimen. However, abortion providers have chosen instead to administer the drug regimen in any way that they want, with the primary consideration seeming to be provider convenience not patient safety. It is reasonable and prudent for the State of Oklahoma to limit the use of this drug to the FDA-approved protocol in the interest of protecting women's health and safety.

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[50] *See* discussion in Proposition 1, § B.2, *supra.*

[51] ACOG Practice Bulletin 67, *supra* note 10; R. Kulier, *Medical Methods for First Trimester Abortion*, *supra* note 14.

PROPOSITION 2:

MEDICAL PROFESSIONALS DO NOT VIEW TREATMENT OF ECTOPIC PREGNANCY AS AN ABORTION. IN THE MEDICAL COMMUNITY, "PREGNANCY" IS DEFINED AS BEGINNING WHEN AN EMBRYO IMPLANTS IN THE UTERUS.

The Act does not prohibit the use of methotrexate to treat ectopic pregnancies. Besides Mifeprex, other drugs can be used to induce abortion, including "Plan B," cytotec, methotrexate, and Ella (whose chemical makeup is similar to mifepristone). Methotrexate is a Folic Acid inhibitor.[52] Like many drugs, it has several uses. It is used in chemotherapy to kill rapidly dividing cells. It can also be used to terminate a pregnancy, but is more effective in treating an early ectopic pregnancy. The Oklahoma law does not cover all drugs, including methotrexate, but applies only when the drug is used with the *intent* to induce an abortion.[53]

Within the medical community, both nationwide and in Oklahoma, treatment of an ectopic pregnancy and termination of a pregnancy (abortion) are two distinct procedures, because an ectopic pregnancy is not considered a pregnancy. For example, the Guttmacher Institute, quoting ACOG, has explained:

> To be sure, not every act of intercourse results in a pregnancy. First, ovulation (i.e., the monthly release of a woman's egg) must occur. Then, the egg must be fertilized. Fertilization describes the process by which a single sperm gradually penetrates the layers of an egg to form a new cell ("zygote"). This usually occurs in the fallopian tubes and can take up to 24 hours. There is only a short window during which an egg can be fertilized. If fertilization does not occur during that time, the egg dissolves and then hormonal changes trigger

[52] FOOD & DRUG ADMIN., *Final Printed Label: Methotrexate Sodium for Injection*, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/11719slr106_methotrexate_lbl.pdf (last visited Aug. 13, 2013).

[53] *See* OKLA. STAT. tit. 63, § 1-729(a)(A)(1).

> menstruation; however, if fertilization does occur, the zygote divides and differentiates into a "preembryo" while being carried down the fallopian tube toward the uterus. Implantation of the preembryo in the uterine lining begins about five days after fertilization. Implantation can be completed as early as eight days or as late as 18 days after fertilization, but usually takes about 14 days. Between one-third and one-half of all fertilized eggs never fully implant. *A pregnancy is considered to be established only after implantation is complete.*[54]

This definition from Guttmacher, quoting ACOG clearly implies that pregnancy does not begin until implantation of the embryo in the lining of the uterus is completed.

Therefore, since "elective abortion" is the "termination of a pregnancy," and since a "pregnancy" does not exist until completion of implantation of the embryo in the lining of the uterus, it is clear that the straightforward and common medical understanding of "elective abortion" is the termination of an intrauterine pregnancy.

This definition of pregnancy is widely supported across the medical community. For example, the Food and Drug Administration assigns five pregnancy categories for use in drug formularies, all of which contemplate only uterine pregnancies.[55] The Center for Reproductive Law and Policy says, "Pregnancy begins when the fertilized egg is implanted in the woman's uterine wall."[56] Further, Planned Parenthood states,

> According to the general medical definitions of pregnancy that have been endorsed by many organizations — including the American College of Obstetricians and Gynecologists and the

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[54] Rachel Benson Gold, *The Implications of Defining When a Woman Is Pregnant*, GUTTMACHER INST. (May 2005), *at* http://www.guttmacher.org/pubs/tgr/08/2/gr080207.html (emphasis added).

[55] *FDA Pregnancy Categories*, *available at* http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf (last accessed Aug. 9, 2013).

[56] Center for Reproductive Law & Policy, *Emergency Contraception: An Important Component of Women's Rights* (Feb. 1999), *available at* http://www.familycareintl.org/UserFiles/File/pdfs/CRLP_EC.pdf.

> United States Department of Health and Human Services — pregnancy begins when a pre-embryo completes implantation into the lining of the uterus.[57]

Thus it is clear that since an ectopic pregnancy is by definition an embryo which has implanted OUTSIDE of the lining of the uterus, an ectopic pregnancy does not fall into the common definition and usage of the term "pregnancy" as it pertains to abortion, which is defined as a termination of pregnancy. As such, this Act has no bearing on the use of methotrexate to treat ectopic pregnancies.

CONCLUSION

The Act reflects sound medical evidence which demonstrates that the FDA-approved Mifeprex Regimen is safer than off-label uses. Since surgical abortion is always available as an option throughout the first trimester, and since it is safer and faster than medical abortion, the State's restriction of medical abortions from 63 to 49 days poses no undue burden on access to abortion. Further, since treatment of ectopic pregnancy is not considered to be an abortion procedure by the medical community, the Act's regulation of medical abortions has no bearing on the use of methotrexate to treat ectopic pregnancies. Consequently, the Act poses no undue burden on abortion and does not otherwise impact women's access to healthcare.

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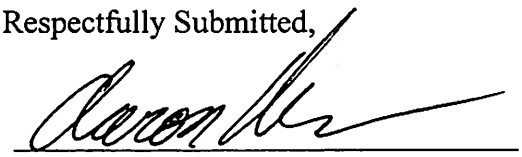
[57]Planned Parenthood Federation of America, *The Difference Between the Morning-After Pill and the Abortion Pill* (Jan. 2012), *available at* http://www.plannedparenthood.org/files/PPFA/Difference_Between_Morning_After_Pill.pdf (citing, *inter alia*, ACOG, *Statement on Contraceptive Methods* (1998); 45 CFR 46.203).

Respectfully Submitted,



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I hereby certify that on the ~~15th~~ 20th SBC day of August, 2013, a true and correct copy of the foregoing instrument was sent by email and U.S. mail, postage prepaid to the following:

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