ALLIANCE DEFENDING
FREEDOM
FOR FAITH FOR JUSTICE

August 21, 2013

Via U.S. Mail and Email: Mark.bowden@iowa.gov

Mark Bowden
Executive Director
Iowa Board of Medicine
400 SW Eighth Street, Suite C
Des Moines, Iowa 50309-4683

Re: Proposed Rule ARC 0891C to Amend IAC 653 – Chapter 13 to Establish Standards of Practice for Physicians who Prescribe or Administer Abortion-inducing Drugs

Dear Mr. Bowden:

On behalf of the American Association of Pro-life Obstetricians & Gynecologists ("AAPLOG") and Alliance Defending Freedom, we express our strong support for the "Petition for Rulemaking Regarding the Standards of Practice for Performing a Chemical Abortion" submitted by Dr. Susan Beck and 14 other healthcare providers and which we are informed is scheduled to be heard by the Iowa Board of Medicine on August 28, 2013.

AAPLOG is a recognized medical professional interest group of the American College/Congress of Obstetricians and Gynecologists (ACOG) and current represents over 2,000 obstetricians and gynecologists throughout the United States.

Alliance Defending Freedom is an alliance-building legal ministry that defends and advocates for the right of people to freely live out their faith. Alliance Defending

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Freedom and its 300 allied organizations and 2,200 allied attorneys defend religious liberty, the sanctity of life, and marriage and the family.

We commend the physicians and other medical professionals who have felt compelled to petition the Iowa Board of Medicine for this regulation. They propose to hold physicians to an appropriate standard of care for women in Iowa in connection with the provision of chemical abortions. The proposed regulation would require physicians to physically examine the woman and determine the age and intrauterine location of the pregnancy; be present when the abortion-inducing drug is provided to the woman; and schedule a precautionary follow-up appointment with the women twelve to eighteen days after the abortion.

As reported by Alliance Defending Freedom client Susan Thayer, a former Iowa Planned Parenthood clinic manager turned whistleblower, in 2008, Planned Parenthood of the Heartland based in Des Moines, Iowa, began experimenting with webcam abortions in Iowa.

Apparently concerned more with its bottom line than with the health and safety of its female patients, the regime implemented by Planned Parenthood of the Heartland consisted of a woman going to a clinic in a remote area of Iowa which was not staffed by a licensed clinician or physician. A physician in another location, usually Des Moines, would ask the woman a few questions via an Internet webcam connection, then presses a button to open a drawer in front of the woman whereupon the abortifacient drugs mifepristone and misoprostol were released to the woman.

The client was then remotely instructed to take the first set of pills at the clinic, and the second pill 24-48 hours later. The patient was told either at that time or at a later time that, if the patient experienced post-chemical abortion side effects, as there was no physician on site at the Planned Parenthood clinic, the patient should report to her local hospital emergency room and falsely report that she was experiencing a "miscarriage." When this anonymous, Internet-based chemical abortion dispensing process was introduced in Iowa, the number of Iowa abortion clinics ballooned from five to 17.[1]

Webcam abortions represent a significant deviation from the FDA protocol for administration of mifepristone and misoprostol abortions. This deviation represents serious breaches of patient safety and should rightly be prohibited. These safety breaches include:

1. Administration of mifepristone without an adequate evaluation of contraindications to the drug. These contraindications include:
   a. Inability to accurately assess gestational age of the pregnancy. Failures and complications of mifepristone abortion increase with increasing gestational age as discussed in subsequent paragraphs.

[1] http://www.lifenews.com/2013/05/07/missouri-senate-approves-ban-on-dangerous-webcam-abortions/.

b. Inability to rule out ectopic pregnancy. The symptoms of a mifepristone abortion mimic the symptoms of a rupturing ectopic pregnancy. Mifepristone is ineffective in treating ectopic pregnancy. So, if a woman with an ectopic pregnancy is given mifepristone, the ectopic pregnancy can cause rupture of the fallopian tube, bleeding, severe pain, or death. In the United States, as of April 30, 2011, *despite the clear warnings of contraindication,* at least 58 women with ectopic pregnancies had been given mifepristone.[2] Of those women, at least two bled to death from an undiagnosed ectopic pregnancy, presumably after experiencing the cramps, abdominal pain, and perhaps vaginal bleeding expected in a mifepristone abortion. .[3]
c. Inability to assess physical contraindications such as pelvic infections, ovarian masses, cardiac arrhythmias, liver abnormalities etc.

2. Administration of mifepristone and misoprostol by protocols not tested by FDA for safety. These off label protocols include methods of administration which have been linked to patient deaths from overwhelming sepsis by Clostridial organisms. No deaths have been linked to FDA protocol.

FDA approved mifepristone under a special code section used for drugs that "can be safely used only if distribution or use is restricted."[4] In other words, FDA recognized mifepristone's inherent danger, and only approved it with restrictions on its use.[5]

The label for RU-486 reflects 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

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[2] http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf.

[3] http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf.

[4] 21 C.F.R. § 314.520; http://www.gao.gov/new.items/d08751.pdf.

[5] http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf; http://www.cwfa.org/ru486/Citizen%20Petition_Mifeprex%208.20.02.pdf (pp. 4-5).

> 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.[6]

The Final Printed Label calls for a series of three visits.[7] On Day One, the label calls for administration of Mifeprex in a single oral dose of three 200 mg tablets (600 mg)

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[6] Food & Drug Admin., *Mifeprex Final Printed Label*, *supra* note **Error! Bookmark not defined.**.

[7] The label reads:

> Day One: Mifeprex Administration
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> 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.
>
> 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

of Mifeprex.[8] 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 then takes two 200 μg tablets (400 μg) of misoprostol orally."[9] Additionally, the patient is instructed to "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."[10]

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."[11] The implication of this statement is that of all women who present with a desire for early abortion, only a subset of those women properly 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

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> 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.

[8] *Id.*

[9] *Id.*

[10] *Id.*

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

> of cramping and bleeding and should indicate that, rarely the process may not be completed in several weeks.[12]

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"[13] and requires "patient participation throughout a multiple-step process."[14] 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.

The FDA-Approved Protocol Best Protects Women's Health and Safety.

The FDA protocol differs from off-label regimens used in webcam abortions in three important ways. First, the FDA-approved protocol limits its use to 49 days gestation. Secondly, the FDA-approved protocol and the off-label uses call for different dosages and methods of administration of the drugs given. Thirdly, the FDA-approved protocol requires that the patient be seen and evaluated by a professional 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.**

At the time FDA approved the Mifeprex Regimen, 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 FDA-approved protocol has the same efficacy as any off-label protocol.[15] In the interest of the safety of women, however, FDA limited use of the medical abortion

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[12] *Id.*

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

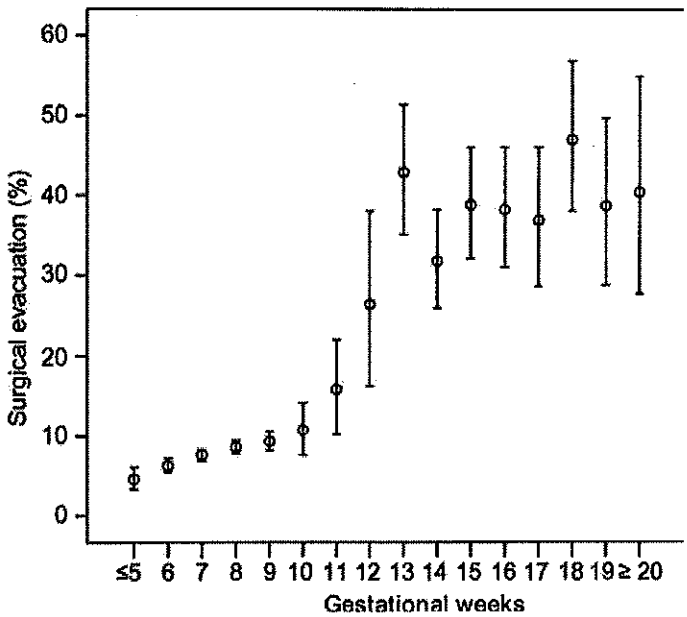
[14] *Id.*

[15] *See* ACOG Practice Bulletin 67; Kulier, R. 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).

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.

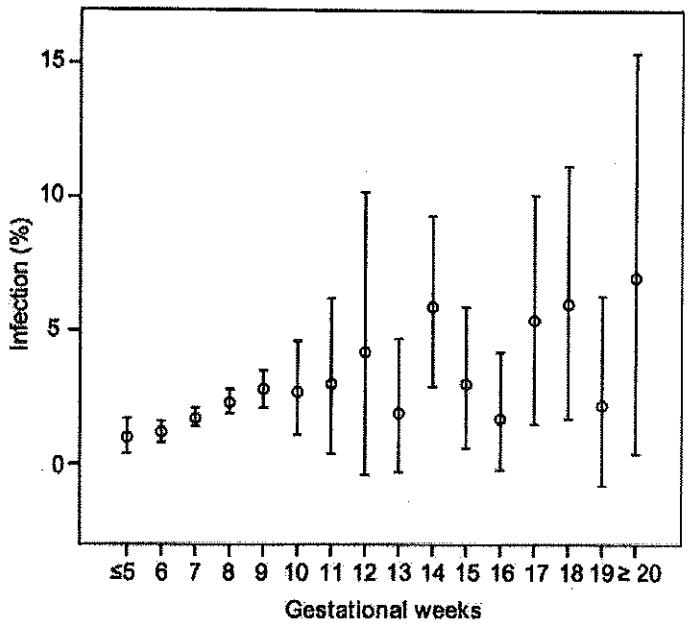
Medical literature documents that medical abortions decline in efficacy and safety after 49 days gestation, thus supporting the FDA's decision to limit use of the Mifeprex Regimen to 49 days or less.

At gestational ages over 49 days, the complications from medical abortion increase regardless of the regimen used.[16] Recently, one study[17] 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. There is an increased rate of both surgical re-evacuation and infection in medical abortions with off-label mifepristone/misoprostol regimens:



[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).



It was because of the increase in complications after 49 days for all regimens of medical abortion that FDA limited use of the Mifeprex Regimen to 49 days or less. Though 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.

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 complete abortion rate at 49 days was 97.5% as compared to the complete abortion rate at 50-56 days, which was 89.3%. Similarly, the ongoing pregnancy rate at 49 days or less was 0.6% versus an ongoing pregnancy rate of 7.1% at 50-56 days gestation. And finally, the rate of need for surgery for failures was 1.9% at 49 days or less compared with 3.6% at 50-56 days gestation.[18]

Other studies 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.[19] A 2011 study found that 5.7% of women using Mifeprex required readmittance to a hospital while only 0.4 percent of patients

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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] Jensen, *supra* note **Error! Bookmark not defined.**, *at* 156 (finding that a higher percentage of RU-486 patients experienced failure (18.3%) than those who had surgical abortions (4.7%)).

required readmittance after surgical abortion.[20] Additional research found similar results (failure rates for medical abortion (5.2–16.0%) exceeded those of surgical abortion (0–4.0%).[21] "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."[22] Other studies found that complications of medical abortion were severe enough that between 13–15% of women obtaining them consulted their general practitioner afterwards.[23] In addition, recent studies in mice raise concern about the effects of mifepristone abortions on the outcomes of subsequent pregnancies.[24] 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.[25]

Thus, the implementation of a medical abortion requires that the patient be available for follow-up in the likely event that some complication will occur which requires further medical care. The argument that webcam abortions provide an opportunity to administer medical abortions in regions without medical infrastructure is increasing the risk to women who will have these complications, but be unable to assess medical care because of their remote region. If a patient is in a remote region, it is better for her to have a surgical abortion which requires a single visit, and is less likely to result in serious or life-threatening complications.

In short, limitation of the option of medical abortion to gestations less than 49 days was a decision 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[26] on an emergency basis

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

[21] 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).

[22] Jensen, *supra* note **Error! Bookmark not defined.**, *at* 153.

[23] 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).

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

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

[26] As per the requirements of:

in every situation 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 selected carefully chosen women, who have access to medical services for serious or life threatening complications but surgical abortion is the less risky standard.

By virtue of Alliance Defending Freedom's representation of Susan Thayer, a former Planned Parenthood of the Heartland clinic director, we have been made aware that most of those Iowa Planned Parenthood of the Heartland clinics which utilize webcam abortions are open during limited hours, have no healthcare professionals on site, and thus no healthcare professional ever sees the patient. The patient is "seen" by a healthcare professional just once, *i.e.,* during the initial visit for a few moments and remotely via skype or another internet webcam arrangement. The patient is told to take the second dosage at home and 24 to 48 hours later. The patient is never seen thereafter by a healthcare professional unless there is a post-medical abortion problem and, in that event, Planned Parenthood personnel regularly refer those women who encounter post-medical abortion problems to the emergency room of a nearby hospital. In addition, we have been made aware that Planned Parenthood of the Heartland makes it a regular practice to provide women with dosages of mifepristone and misoprostol at up to 63 days gestation. Indeed, we understand that Planned Parenthood spokesman Dr. Tom Ross recently informed the Board or others that Planned Parenthood administers mifepristone and misoprostol at up to 70 days gestation.

Planned Parenthood's failure to have a healthcare professional administer the second dosage or to personally examine the patient thereafter is inconsistent with approved FDA guidelines and appropriate standards of care. In addition, if, in fact, Planned Parenthood is administering mifepristone and misoprostol as late as either 63 or 70 days gestation, this practice would also be inconsistent with approved FDA guidelines and appropriate standards of care.

We urge the Board to be sure that, in addition to the procedures required by the proposed regulation, the Board take steps to assure that Planned Parenthood of the Heartland is complying with the 49 day limitation and is not referring patients to hospital emergency rooms and urging such patients to present false information.

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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 11, *at* 6.

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 μg 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.[27] 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 exposure is necessary to compensate for the lesser amount of mifepristone given in the off-label protocols.[28]

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.[29]

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 recently implicated in the

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[27] *See* K. Gemzell-Danielsson, et al., *Comparison Between Oral and Vaginal Administration of Misoprostol on Uterine Contractility*, 93 OBSTET GYNECOL. 275 (1999); EA 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).

[28] *See* B. Winikoff, et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Controlled Trial*, *supra* note 15.

[29] FOOD & DRUG ADMIN., *Final Printed Label: Cytotec (misoprostol)*, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19268slr037.pdf (last visited Aug. 9, 2013).

massive fatal infections seen after some medical abortions.[30] 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.[31] In addition, fatal sepsis has been seen after use of vaginal misoprostol alone, without mifepristone.[32] 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.[33]

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[30] *See* DM Aronoff, et al., *Misoprostol Impairs Female Reproductive Tract Immunity Against Clostridium Sordelli*, 180 J. IMMUNOL. 8222 (2008); Spitz, *supra* note **Error! Bookmark not defined.**, at 444 ("It has been shown in rats that intrauterine misoprostol increases mortality from *C. sordellii* infection by impairing the immune response.").

[31] AL 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).

[32] *See* Cohen, *Toxic Shock Associated With Clostridium sordellii and Clostridium perfringens After Medical and Spontaneous Abortion*, *supra* note 31; Soper, *Abortion and Clostridial Toxic Shock Syndrome*, *supra* note 31, *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.").

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

In contrast, there have been no deaths from the FDA protocol. [34]

Misoprostol is itself indicated as a cause of the massive infections seen with off-label use of the medical abortion,[35] and the increased 800 microgram dose of misoprostol is associated with deaths from C 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".[36]

There have also been reports of massive lethal infections from the use of misoprostol alone, without mifepristone.[37]

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[34] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111328.htm

[35] *See* Dempsey, *Serious Infection Associated With Induced Abortion in the United States*, *supra* note 33, *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 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*.").

[36] DM Aronoff, et al., *Misoprostol Impairs Female Reproductive Tract Immunity Against Clostridium Sordelli*, 180 J. IMMUNOL. 8222 (2008).

[37] *See* Cohen, *Toxic Shock Associated With Clostridium sordellii and Clostridium perfringens After Medical and Spontaneous Abortion*, *supra* note 31; Soper, Abortion and Clostridial Toxic Shock Syndrome, *supra* note 31.

Exposing women to a higher dose of misoprostol is a safety concern raised by the webcam abortion protocols. 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 of misoprostol administrations.[38] 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 seen with the FDA protocol.

Planned Parenthood apparently recognizes the concern and danger from higher misoprostol doses.[39] Reportedly, Planned Parenthood is now experimenting with high dose buccal/sublingual misoprostol. However, the FDA has also reported a death from 800 μg of buccally administered misoprostol.[40]

In 2010, the CDC published comments on Planned Parenthood's use of 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.[41]

However, it is reported by Alliance Defending Freedom client Susan Thayer that Planned Parenthood's Iowa clinics continue to administer high dosage unites of misoprostol, all without the physical presence of a licensed healthcare professional.

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[38] *See* Gemzell-Danielsson, *supra* note 27; Schaff, *supra* note 27; Zieman, *supra* note 27.

[39] *See* M. Fjerstada, 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.

[40] *See* EA Schaff, *Mifepristone Review 10 Years Later*, *supra* note 27.

[41] Meites E, Zane S, Gould C. *Fatal Clostridium Sordellii Infections after Medical Abortions.* 363 N. ENG. J. MED. 1382 (2010).

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 reasonable for the State 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.

The FDA-approved protocol's requirement that the patient be seen and evaluated for completion of the abortion before being given misoprostol minimizes exposure to unnecessary drugs and protects women's health and safety.

Finally, the FDA regimen differs from webcam 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[42] (and 2–3% percent will complete with mifepristone alone within two days of ingestion),[43] 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 WHO 2003 Tech 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 conception."[44] Subsequent studies confirm similar rates of rapid completion of pregnancy termination.[45] 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

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42 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111328.htm.

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

44 WORLD HEALTH ORGANIZATION, SAFE ABORTION: TECHNICAL AND POLICY GUIDANCE FOR HEALTH SYSTEMS 37 (2003).

45 *See e.g.,* El-Refaey, *Induction of Abortion with Mifepristone (RU-486) and Oral or Vaginal Misoprostol, supra* note 43; 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).

observation period is not explicitly required by the FDA protocol, but it is implied by the ACOG Practice Bulletin 67.[46]

Documentation of completion of the abortion at this second visit would then 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% 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[47] and can cause significant deformities in fetuses exposed to the drug.[48] 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, with the idea that the visit times will provide important information to the patient and abortion provider, and minimize 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

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[46] ACOG Practice Bulletin 67, *supra* note 11, at Table 1: Advantages and Disadvantages.

[47] *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).

[48] *See* FOOD & DRUG ADMIN., *Final Printed Label: Cytotec (misoprostol)*, *supra* note 29. *See also* CH Gonzales, et al., *Congenital Abnormalities in Brazilian Children Associated with Misoprostol Misuse in First Trimester Pregnancy*, 351 LANCET 1624 (1998); ES Opaleye, et al., *Evaluation of the Teratogenic Risks in Gestations Exposed to Misoprostol*, 32 REV BRAS GINECOL OBSTET. 19 (2010).

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 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.[49]

Unlike the FDA protocol, 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 used in the webcam abortions and the FDA regimen.[50] Thus, 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 safety and efficacy of the regimens and method of administration used for webcam abortions has never been tested. Yet we know that with mifepristone abortions, close follow-up is essential for patient safety because of the rate of serious or life-threatening complications. Webcam abortions have as the primary consideration provider convenience not patient safety. It is reasonable and prudent for the State of IOWA to prohibit the dispensing of mifepristone by webcam in the interest of protecting women's health and safety.

Mifepristone carries with it the risk of extremely severe side effects, including severe and life-threatening bleeding, sepsis infections, heart attack, and death,[51] as well as increased risk of future ectopic pregnancy.[52] These conditions have all impacted real women; as of April 30, 2011, the U.S. Food and Drug Administration ("FDA") had documented 2,207 self-reported "adverse events" in the United States post-marketing – *i.e.*, not during a clinical trial. The adverse events included 14 deaths, 612 hospitalizations, 339 blood transfusions, 48 severe infections, and 208 other infections.[53]

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

[50] Cochrane and ACOG at fn 15, *supra*.

[51] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111328.htm; http://www.fda.gov/downloads/Drugs/DrugSafety/UCM088643.pdf.

[52] Jean Bouyer et al., *Risk Factors for Ectopic Pregnancy: A Comprehensive Analysis Based on a Large Case-Control, Population-Based Study in France*, 157 AM. J. EPIDEMIOL. 185 (2003).

[53] http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf; Margaret M. Gary & Donna J. Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, 40 ANNALS OF PHARMACOTHERAPY (2006).

Worldwide, the number of deaths is at least 28.[54] And of course, these adverse event reports are only voluntarily submitted to the drug company, which then passes on what they feel is significant to the FDA[55]; it is likely that many more "adverse events" will never be known.

A physical exam and ultrasound are absolutely necessary prior to the use of mifepristone in order to determine fetal age and rule out ectopic pregnancy and other contraindications, and again in a follow-up after the use of mifepristone in order to confirm abortion and rule out life-threatening infection.

Both an in-person physical exam and an ultrasound are needed prior to prescription of mifepristone.[56] "[U]ltrasound is the medical gold standard for dating early pregnancy[57] and ruling out ectopic pregnancy"[58]; it is not possible to diagnose ectopic pregnancy at a young gestational age without performing an ultrasound,[59] and a physical examination is additionally required to confirm and to ensure that there are no other contraindications to mifepristone use. Indeed, the mifepristone trials prior to marketing required ultrasound to determine fetal age and location.[60] In-person physical examination

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As AAPLOG noted after this latest Adverse Event Report was published:

> The FDA safety trials a decade ago found that at 7 wks gestational age, 8% of women required a D&C to complete their abortion (because of heavy bleeding or incomplete AB). At 8 wks, 16% required a D&C, and at 9 wks (63 days), 23% required D&C. The FDA protocol recommends Mifeprex be used within the 7 week limit. However, by common off label usage, the drug is used up to 9 wks—and even that is a guess, since ultrasound is not required prior to Mifeprex usage, and "LMP" is a notoriously inadequate way to judge gestational age, often being 1-2 wks off. So many women taking the drug will be in the 23% category for an urgent D&C.

http://www.aaplog.org/american-issues-2/fda-publishes-mifeprex-adverse-events-report/.

[54] http://www.mercatornet.com/demography/view/10501.

[55] http://www.aaplog.org/american-issues-2/fda-publishes-mifeprex-adverse-events-report/

[56] Crenin & Spitz, Use of Various Ultrasonographic Criteria to Evaluate the Efficacy of Mifepristone and Misoprostol for Medical Abortion, 181 AM. J. OF OBSTET. & GYNEC. 1419 (1999); *see also* the 2004 ACOG Compendium of Selected Publications, p. 491 (confirming that vaginal sonography is "the most accurate means of confirming intrauterine pregnancy and gestational age").

[57] http://www.cwfa.org/ru486/Citizen%20Petition_Mifeprex%208.20.02.pdf (pp. 57-60).

[58] http://www.aaplog.org/position-and-papers/mifeprex/aaplog-statement-on-current-practice-mifeprex-the-degradation-of-a-standard-of-care/.

[59] http://www.cwfa.org/ru486/Citizen%20Petition_Mifeprex%208.20.02.pdf (pp. 60-61).

[60] http://www.aaplog.org/position-and-papers/mifeprex/aaplog-statement-on-current-practice-mifeprex-the-degradation-of-a-standard-of-care/.

and ultrasound are vital to ensure fetal age and location; anything less fails Iowa women, and will lead to injuries and potentially even deaths.

While the "standard of care," quite literally, is established by the healthcare providers in a region who treat the same diagnosis, here Planned Parenthood is the source of the majority of the providers. Thus, following the provider-established "standard of care route" would in essence become "whatever Planned Parenthood does." Planned Parenthood must not be allowed to become a law unto itself, singlehandedly driving down the standard of care for women's health because of its near-monopoly on telemed abortion in Iowa.[61] And while a single provider must never be permitted to be the sole determinant of the standard of care, this is particularly true in the case of Planned Parenthood, which has already demonstrated its lack of regard for women's well-being through its off-label use of this very drug.[62] Clearly, telemedicine – while it may be legitimate when it comes to discrete, document-based tasks such as reading X-rays – is not standard of care when it comes to abortion or the management of miscarriage.

The State of Iowa is not alone in this endeavor. Sixteen states have already acted to require prescribing physicians to be in the physical presence of the woman: Alabama, Arizona, Indiana, Kansas, Louisiana, Michigan, Mississippi, Missouri, Nebraska, North Carolina, North Dakota, Oklahoma, South Dakota, Tennessee, Texas, and Wisconsin.[63]

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[61] http://abortiondocs.org/search-results/?state=IA.

[62] http://www.aul.org/2013/01/planned-parenthood%E2%80%99s-latest-%E2%80%9Cstudy%E2%80%9D-proves-nothing-about-the-%E2%80%9Csafety%E2%80%9D-of-ru-486/. In addition to experimentation with dosage amounts and times, and clinic vs. home location of administration and delivery, mifepristone prescribers have begun to experiment with off-label *vaginal* – as opposed to the approved oral – administration of mifepristol's companion drug misoprostol (which was never permitted to be marketed for abortion at all). This back-alley "care" has resulted in more deaths: "Since the approval of Mifeprex in September 2000, FDA has been informed of eight deaths in the United States due to serious infections following medical abortion with mifepristone and misoprostol . . . . In all but one case, the misoprostol was used intravaginally." Vaginal administration has led to other serious complications, as well: "In many of the[] cases of adverse effects, misoprostol was given vaginally, not orally . . . ."

FDA's response is lacking and indicates that it is, indeed, up to state Boards of Medicine to ensure women's safety:

> FDA is aware that medical practitioners may be using modified regimens, including . . . advising the woman that the oral misoprostol tablets may be inserted into the vagina. While some of the modified regimens have been well described in the literature, the safety and effectiveness of Mifeprex dosing regimens, other than the one approved by FDA, including use of oral misoprostol intravaginally, has not been established by the FDA.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111328.htm.

[63] Safety precautions are already in effect in eleven of those states. The laws in Missouri, North Carolina, and Texas are scheduled to go into effect later in 2013. The laws in North Dakota and Wisconsin are currently enjoined by court order.

These laws are being enacted in states that are expressly concerned with the health and safety of women and without regard to biases for or against abortion.[64]

One final comment we wish to make, though it may not be within the ambit of the Board's authority, has to do with the need for there to be a waiting period in the State of Iowa for a woman seeking an abortion. Because there is currently no waiting period in the State of Iowa, we have been informed that many women who enter a Planned Parenthood clinic seek a urine pregnancy test which takes about three minutes. If the woman thereupon learns she is pregnant, Planned Parenthood personnel urge the woman to proceed to have an abortion at that time. Many women in this position are very vulnerable and do not think they have any viable alternative. They become convinced that a medical abortion is an "easy way out" of a very difficult situation and are persuaded by Planned Parenthood personnel to act without having time to really think through their decision. We are informed that, later, many women report deep regret at having made such an important decision without time to really think through the consequences of the decision.

We urge the Iowa Board of Medicine to adopt these common-sense regulations.

Sincerely,

Donna Harrison

Donna Harrison, M.D.
Executive Director
American Association of Pro-Life
Obstetricians and Gynecologists

Michael J. Norton
Senior Counsel
Catherine Glenn Foster
Litigation Counsel
Alliance Defending Freedom

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[64] *See, e.g.*, http://www.lifenews.com/2013/07/12/missouri-gov-nixon-allows-pro-life-webcam-abortion-ban-to-become-law/.