ISSUE BRIEF

The FDA Adopts the Abortion Industry Standards for the Mifeprex® (RU-486) Abortion Regimen

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On March 30, 2016, the U.S. Food and Drug Administration (FDA) announced changes to the labeling for the Mifeprex® (RU-486) abortion regimen.[1] With these modifications, the FDA accepted wholesale the "off-label" regimen now being used by abortion providers like Planned Parenthood. These changes will greatly lower the already inadequate safety standards that had been put in place when the drug was first approved by the Clinton FDA in 2000. Below this brief description and initial analysis of the changes approved by the FDA, FRC summarizes the most recent adverse event data available, an FDA report from 2011, of the Mifeprex® abortion regimen.

MAJOR CHANGES TO THE ABORTION DRUG REGIMEN

There were four major changes to the drug regimen approved by the FDA on March 30, 2016:

- **Dosage of both drugs changed.** The dosages of the two drugs have been changed. Previously, the patient started the abortion process by taking three mifepristone tablets of 200 mg each—for a total of 600 mg. Now, the dosage of mifepristone has been reduced to one third of the original regimen; the patient will take only one tablet of 200 mg. Mifepristone is expensive and this may be a way for the industry to make a profit with the lowest costs. In the original regimen, 24 to 48 hours after taking the mifepristone, the patient would take two misoprostol tablets of 200 mcg each for a total of 400 mcg. That dosage has been increased to four misoprostol tablets of 200 mcg totaling 800 mcg, doubling the total dosage. Taking misoprostol should not occur later than 48 hours after mifepristone ingestion. FDA notes that the regimen's effectiveness may be reduced if the misoprostol "is administered less than 24 hours or more than 48 hours after the mifepristone administration."[2]

- **Method for misoprostol ingestion changed.** In the new regimen the method by which misoprostol is taken has changed and now reflects abortion industry practice. In 2000, the FDA-approved labeling indicated that the misoprostol tablets were to be taken orally—that is, they were to be swallowed. However, routine off-label administration of misoprostol was vaginal in the United States until reports and cases of a severe infection with *Clostridium sordelli* prompted safety concerns.[3] Within the past ten years it has become commonplace for misoprostol to be

[1] The Mifeprex® abortion regimen consists of the use of two drugs. Mifepristone (RU-486) is first taken to block the body from maintaining the pregnancy. Then, a second drug, misoprostol, is used to expel the remains of the embryo or fetus.
[2] Mifeprex Label (2016) at 3, http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. For more information, see Medication Guide (2016): http://www.fda.gov/downloads/Drugs/Drugsafety/ucm088643.pdf.
[3] The 2011 FDA summary lists that out of 14 U.S. reported deaths, 8 cases involved sepsis: 7 cases tested positive for *Clostridium sordelli* and 1 case for *Clostridium perfringens.* All but one fatal sepsis case reported vaginal misoprostol administration; one case reported buccal misoprostol administration.

taken by the buccal route (pronounced "buckle"), that is, two tablets placed between the cheek and gum on the left side of the mouth while doing the same on the right side until the tablets are dissolved.[4] The new FDA-approved labeling indicates that patients now will take the four misoprostol tablets (4 x 200 mcg) buccally.

- **Timeframe for starting the regimen is extended by three weeks.** FDA approved a patient's starting the regimen as late as 70 days into a pregnancy as determined by gestational age. Gestational age is measured from the first day of the woman's last menstrual cycle to the current date. The FDA approval in 2000 allowed the mifepristone-misoprostol regimen to begin until the 49th day of pregnancy—no later. However, there are very few studies showing the safety and efficacy of RU-486 from 63-70 days gestation. A July 2015 comprehensive survey of the buccal misoprostol abortion regimen noted, "Another obvious limitation of the available data is the relative lack of significant numbers of women who reported using misoprostol beyond 63 days of gestation."[5] The studies done show that the farther along the child is developed, the greater the failure rate for the regimen.[6]

- **Second office visit eliminated.** In the new regimen, misoprostol may be self-administered by the patient without a second visit to the physician.[7] A final follow-up is recommended 7-14 days after the patient has taken the mifepristone.[8] This puts a woman at greater risk, since she is not monitored for sepsis (infection), hemorrhage, ectopic pregnancy, and other complications.[9]

THE FDA MUST RELEASE THE DATA RELIED UPON FOR THE APPROVAL

There is a great deal that has to be investigated and studied concerning the FDA's approval for this far more risky abortion regimen. Of greatest concern is the increased risk to women from the new Mifeprex regimen's increasing ineffectiveness as the pregnancy age increases. For example, according to the newly approved Mifeprex Label, between 64-70 days gestational age, 7.3% of abortions were incomplete and 3.1% required "surgical intervention for ongoing pregnancy."[10] Further, one study presented a 4.1% surgical evacuation rate for 57-63 days gestation.[11] Another study described an intervention rate (non-"success" rate) in 6.5% of abortions from 57-63 days and a 7.2% rate for 63-70 days gestation.[12] That same study showed 3.7% (about 1 in 25) of the patients between 57-63 days and 4.6% (about 1 in 20) of the patients between 64-70 days gestation having a major adverse event requiring going to the emergency room.[13]

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[4] Mifeprex Label (2016) at 3.
[5] Melissa J. Chen and Mitchell D. Creinin, "Mifepristone with Buccal Misoprostol for Medical Abortion: A Systematic Review," Obst and Gynecol. 2015: 126 (1): 12-21, at 20. However, it appears that only two studies were found by Chen and Mitchell with data from Days 64-70. See, notes 15 (Winikoff, 2012) and 16 (Pena, 2014).
[6] Mifeprex Label (2016) at 2.
[7] Mifeprex Label (2016) at 3 compared with Mifeprex Label (rev. 2: 7/19/2005) at 13.
[8] Mifeprex Label (2016) at 4 (sec. 2.3 "Post-Treatment Assessment: Day 7-14").
[9] See 2011 FDA Adverse Event Report for a description of complications.
[10] Mifeprex Label (2016) at 13, Table 4. Even for Days 57-63 the rates are 5.3% (incomplete abortion) and 2% (required surgical intervention) are alarming. At 57 days and later, at least one in fifty women required surgical intervention.
[11] M. Peña et al., "Efficacy and acceptability of a mifepristone-misoprostol combined regimen for early induced abortion among women in Mexico City," Int J Gynaecol Obstet. 2014; 127 (1): 82-5. Table 2.
[12] B. Winikoff et al., "Extending outpatient medical abortion services through 70 days of gestational age," Obstet Gynecol. 2012; 120 (5): 1070-6, Table 2.
[13] Ibid.

The Mifeprex Label refers to 22 supporting studies for the Supplemental NDA (New Drug Application) but does not provide citations to them.[14] This is highly unusual. In the time period in question, the Mifeprex Label, Table 4 refers to four studies (incomplete abortion) and three studies (surgical intervention) but does not provide citations.[15] FRC calls upon the FDA to release the list of studies that were used to support the acceptance of the new Mifeprex regimen and to make that data publicly available. We note that the FDA webpage for the 2016 Supplemental NDA does not contain a "Medical Review" tab containing the FDA's review documents for the approval.[16]

MOST RECENT FDA ADVERSE EVENTS REPORT (APRIL, 2011)

On April 30, 2011 the FDA completed an internal summary[17] of Adverse Events related to Mifepristone. This information was gathered from U.S. post-marketing reports and not from a clinical trial.

The estimated number of women who used mifepristone in the U.S. from September 2000 to the end of April 2011 was approximately 1.52 million women. During that time, there were 2,207 reported cases with adverse events in the U.S., including:

- 14 deaths[18] (including one death reported from buccal misosprostol use)
- 612 hospitalizations
- 58 ectopic pregnancies
- 339 cases of blood loss requiring transfusions
- 256 cases of infections, of which 48 cases were considered severe
    - Infections include endometritis, pelvic inflammatory disease, and pelvic infections with sepsis.
    - The FDA report defined severe infections as generally involving "death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours, total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection."

For a detailed analysis of this FDA document, see an FRC Issue Analysis released in May 2012, "RU-486 (Mifepristone) Side-Effects, 2000-2012."[19]

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[14] Mifeprex Label (2016) at 12 (sec. 14 "Clinical Studies").
[15] Mifeprex Label (2016) at 13, Table 4 (64-70 Days).
[16] Medical Review (2000), Food and Drug Administration, accessed April 18, 2016, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_mifepristone.cfm (Given the dramatic expansion of the regimen with this approval, a similar set of FDA review documents should have been made available).
[17] "Mifepristone U.S. Postmarketing Adverse Events Summary through 04/30/2011," Food and Drug Administration, accessed April 18, 2016, http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf.
[18] There were five additional reported deaths of women outside of the U.S. It should be noted that the total of 19 deaths in no way represents the actual number of deaths, but of *reported* deaths.
[19] Gacek, Christopher. "RU-486 (Mifepristone) Side-Effects, 2000-2012," May 2012, http://downloads.frc.org/EF/EF12F08.pdf.