IN THE SUPREME COURT OF OHIO

NANCY H. ROGERS, OHIO ATTORNEY GENERAL, et al.,	: Case No. 2008-1234
	:
Petitioners,	: On Review of Certified
	: Questions from the U.S.
v.	: Court of Appeals for the
	: Sixth Circuit
PLANNED PARENTHOOD CINCINNATI REGION, et al.,	:
	: U.S. Court of Appeals Case
Respondents.	: Nos. 06-4422/06-4423

BRIEF OF *AMICI CURIAE* MEMBERS OF THE U.S. CONGRESS IN SUPPORT OF PETITIONERS

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STATEMENT OF INTEREST OF *AMICI CURIAE*

The constitutionality of the Food & Drug Administration's (FDA) protocol for the administration of RU-486, or mifepristone, has been called into question in this case. *Amici Curiae* Representatives Roscoe Bartlett (MD),[1] John A. Boehner (OH),[2] Dan Burton (IN),[3] Steve Chabot (OH), Trent Franks (AZ), Jim Jordan (OH), Robert E. Latta (OH), Joseph R. Pitts (PA), Jean Schmidt (OH),[4] and Chris Smith (NJ)[5] are members of the United States Congress who support adherence to the FDA protocol, at a minimum, for the administration of mifepristone. *Amici* have a strong interest in the proper interpretation and administration of a federal law.

Additionally, *Amici* Representatives Burton and Schmidt have a particular interest in ensuring that adolescents and adult women are protected from the medical risks associated with mifepristone. These *Amici* participated in the May 17, 2006, hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Resources, which heard extensive evidence demonstrating the life-threatening risks associated with mifepristone. The Committee's October 2006 Staff Report, which concluded that mifepristone should be withdrawn from the market because of its substantial health risks, is attached as an Appendix to this brief.

The other *Amici*, though not members of the House Subcommittee, share their colleagues' interest in the enforcement of the FDA protocol and their interest in ensuring that

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[1] Lead Sponsor of H.R. 63, the RU-486 Suspension and Review Act.

[2] House Minority Leader.

[3] Member of the House Subcommittee on Criminal Justice, Drug Policy and Human Resources.

[4] Member of the House Subcommittee on Criminal Justice, Drug Policy and Human Resources.

[5] Chairman of the House Pro-Life Caucus.

women are protected from the medical risks, and especially those additional risks incurred by off-label use, of mifepristone.

Amici are deeply concerned that abortionists are admittedly not administering or dispensing mifepristone in accordance with the FDA protocol as outlined in the FDA's approval letter and in the drug's label. As explained herein, adherence to both the FDA's approval letter and the drug's label is clearly required under OHIO REV. CODE § 2919.123.

For these reasons, *Amici* urge this Court to answer the certified questions in the affirmative.

STATEMENT OF FACTS

Amici adopt the statement of facts as outlined by the Petitioners. In summary, abortionists, including Respondents, admittedly administer and dispense the abortion drug mifepristone contrary to the protocol described in the FDA's approval letter for the drug and contrary to the dosage and administration instructions of the drug's label. In response to the dangers posed by the drug and especially by such off-label use, legislators in the State of Ohio enacted OHIO REV. CODE § 2919.123, seeking to require abortionists to administer and dispense the drug according to the protocol dictated by "federal law." As this court is well aware, Respondents argue that, where § 2919.123 requires them to follow "federal law," they do not know what "federal law" means. At the Sixth Circuit, *Amici Curiae* argued that, under controlling Supreme Court and lower court federal jurisprudence, the use of the term "federal law" clearly encompasses the FDA drug approval letter as well as the mifepristone drug label.

The Sixth Circuit certified two questions of state law interpretation by this Court. As outlined in this Court's order of September 10, 2008, this Court will answer the following two questions:

1. Does R.C. 2919.123 mandate that physicians in Ohio who perform abortions using mifepristone do so in compliance with the forty-nine-day gestational limit described in the FDA approval letter?

2. Does R.C. 2919.123 mandate that physicians in Ohio who perform abortions using mifepristone do so in compliance with the treatment protocols and dosage indications described in the drug's final printed labeling?

ARGUMENT

Amici urge this Court to answer the foregoing questions in the affirmative. As demonstrated herein, OHIO REV. CODE § 2919.123 clearly encompasses the FDA approval letter and the mifepristone drug label in requiring abortionists to follow federal protocol. This federal

protocol includes complying with the 49-day gestational limit described in the FDA approval letter, as well as the treatment protocols and dosage indications in the drug's final printed labeling. The FDA's protocol is clear to both parties, and physicians routinely prescribe medications in accordance with federal law. In addition, a reading of the Act as a whole leads to the FDA-approved mifepristone label, which sets out the FDA protocol.

In addition, the severe medical risks of mifepristone underscore the importance of § 2919.123. These risks demonstrate the danger of off-label use of mifepristone and the need for the standard of care found in § 2919.123—including compliance with the FDA approval letter and the drug's label.

Proposition of Law No. I: OHIO REV. CODE § 2919.123 clearly encompasses the FDA approval letter and the mifepristone drug label in requiring abortionists to follow "federal law"

A. Ohio and federal court jurisprudence support common sense interpretation of laws

Respondents have argued that OHIO REV. CODE § 2919.123 is vague, particularly as it requires physicians to follow "federal law,"[6] and that they do not know what "federal law" means. Yet both Ohio and U.S. Supreme Court jurisprudence support common sense interpretation of laws. A statute must simply "give the person of ordinary intelligence a reasonable opportunity to know what is prohibited, so that he may act accordingly." *Grayned v. City of Rockford*, 408 U.S. 104, 108 (1972); *see also State v. McKnight*, 837 N.E.2d 315, 352 (Ohio 2005) (stating that a criminal statute must only define a criminal offense with sufficient clarity for an ordinary person to understand). Statutory language need not provide

[6] OHIO REV. CODE § 2919.123(A) states that physicians must provide mifepristone "in accordance with federal law." "Federal law" is defined to mean "any law, rule, or regulation of the United States or any drug approval letter of the food and drug administration of the United States that governs or regulates the use of RU-486 (mifepristone) for the purpose of inducing abortions." *Id.* at § 2919.123(F)(1).

"mathematical certainty." *Grayned,* 408 U.S. at 110; *State v. Williams*, 728 N.E.2d 342, 361 (Ohio 2000). Under both Ohio and federal court precedent, the common sense interpretation of "federal law" in § 2919.123 includes the FDA approval letter as well as the mifepristone label.

1. Ohio Court Precedent

Under Ohio law, a criminal statute must simply give a person of ordinary intelligence who seeks to avoid its penalties fair notice of the conduct required or prohibited. *See, e.g.*, *McKnight*, 837 N.E.2d at 352; *City of Norwood v. Horney*, 853 N.E.2d 1115, 1142 (Ohio 2006); *State v. Dorso*, 446 N.E.2d 449, 450 (Ohio 1983). Statutes need not define every word or phrase used with "mathematical certainty;" instead, it is only necessary that a person of common intelligence be able to determine what conduct is prohibited. *Williams*, 728 N.E.2d at 361.

In fact, a "legislative body need not define every word it uses in an enactment." *State v. Dorso*, 446 N.E.2d at 451. Further, "any term left undefined by statute is to be accorded its common, everyday meaning." *Id.* "Words in common use will be construed in their ordinary acceptation and significance and with the meaning commonly attributed to them." *Id.*

Examples in Ohio abound demonstrating that the law does not demand extreme specificity in statutes, and that verbiage used which would not likely "confound the person of ordinarily intelligence" is perfectly acceptable and should be given the meaning understood by the community affected by the statute. In *State v. Dorso*, this Court examined a noise ordinance which prohibited disturbing the peace and quiet in a neighborhood. *Dorso*, 446 N.E.2d at 450. The appellee was charged with violating the rule and subsequently claimed he did not understand the word "neighborhood." *See generally, id.* The court disagreed, holding that the word "neighborhood" should be given its ordinary meaning, and stating that the definition of "neighborhood" was well within the appellee's own comprehension. *Id.* at 451.

Furthermore, when a statute is aimed at regulating the medical community, terminology is to be given the meaning understood by the medical community—and the medical community cannot claim it misunderstands words or phrases or instructions routinely used in the medical community. For example, in *Founder's Women's Health Center v. Ohio State Department of Health*, the court considered a dispute regarding whether certain abortion clinics constituted "ambulatory surgical facilities" under state law. 2002 Ohio App. LEXIS 4345 (Ohio Ct. App. 2002). The Department of Health had visited and determined that the appellant clinics did in fact constitute ambulatory surgical centers that must be licensed as such. *See generally, id.* At issue was whether the clinics were "offices of private physicians" under OHIO REV. CODE § 3702.30, because, the clinics claimed, if they were considered offices of private physicians, they could not be regulated as ambulatory surgical centers. *Id.* In litigating this argument, the clinics claimed that, because the statute did not define "offices of private physicians," the phrase was vague. *Id.*

"Offices of private physicians" was not defined under OHIO REV. CODE § 3702.30. In determining its meaning, the appellate court first quoted Ohio Supreme Court precedent for the rule of construction that terms used in a statute must be given their usual and ordinary meaning. *Id.* at *32 (citing *Leon v. Ohio St. Bd. of Psychology*, 590 N.E.2d 1223 (Ohio 1992)). The court also reiterated the standard: men of common intelligence must not be left to guess at a term's meaning. *Id.* at *33. However, the court specifically applied this standard to the context of the medical profession, holding that members of the medical profession should understand what is meant by the phrase "offices of private physicians." *Id.* at **33-34. Thus, when determining the meaning of a word or phrase used in a statute, the community affected by the statute is the appropriate community to use in evaluating the meaning of that statute. In other words, in examining a law aimed at the medical profession, the proper evaluation is what definition a

person in the medical profession would assign to a given word or phrase, as is routinely used by the medical community.

2. U.S. Supreme Court and Lower Federal Court Precedent

Because the questions before this court concern the interpretation of a phrase in an abortion-related statute, it is instructive to examine how the U.S. Supreme Court has interpreted words and phrases in abortion-related legislation. In *U.S. v. Vuitch*, the Court heard the appeal of a defendant who had been indicted for producing and attempting to produce an abortion in violation of a D.C. statute. 402 U.S. 62, 67 (1971). A district judge ruled the law unconstitutionally vague, in part because of the "ambivalent and uncertain word 'health'" in the statute's exception clause. *Id.* at 68. The judge stated that there was "no indication whether it include[d] varying degrees of mental as well as physical health." *Id.* at 71.

The Supreme Court disagreed. *Id.* at 71-72. While the legislative history and House Report provided no guidance, one district court judge had construed the word to also include mental health. *Id.* The Court concluded that that construction accorded with the general usage and modern understanding of the word "health," noting that the consideration of "whether a particular operation is necessary for a patient's physical or mental health is *a judgment that physicians are obviously called upon to make routinely* ...." *Id.* at 72 (emphasis added).

The Court affirmed this position in *Doe v. Bolton*, 410 U.S. 179 (1973), the companion case of *Roe v. Wade*, 410 U.S. 113 (1973). The appellants challenged as vague a provision making it a crime to perform an abortion unless the abortion was "necessary." *Bolton*, 410 U.S. at 191. The Court stated, "[w]hether, in the words of the Georgia statute, 'an abortion is necessary' is a professional judgment that the Georgia physician *will be called upon to make routinely*." *Id.* at 192 (emphasis added). Further, interpreting the law in such a way

"*operate[ed] for the benefit, not the disadvantage*, of the pregnant woman." *Id.* (emphasis added).

In interpreting other abortion-related statutes, lower federal courts have also stated that physicians are uniquely suited to understand what is required of them under medically-related laws. For example, in *Karlin v. Foust*, the Seventh Circuit took special note that physicians are highly trained, intelligent persons, and that it was "simply not that difficult" to ascertain what information the informed consent law at issue required them to disseminate. 188 F.3d 446, 477 (7th Cir. 1999). With a "minimum amount of diligence," a physician would have no difficulty complying. *Id.*[7]

In upholding abortion clinic regulations in *Greenville Women's Clinic v. Commissioner, S.C. Department of Health and Environmental Control*, the Fourth Circuit concluded that a "reasonable person, reading the regulation in its entirety and in the context of South Carolina statutes, would be able to interpret the regulation and determine what is required and what conduct is prohibited." 317 F.3d 357, 366 (4th Cir. 2002), *cert. denied*, 538 U.S. 1008 (2003). For example, in examining a provision requiring physicians performing abortions to be "properly qualified," the court outlined that physicians routinely hold themselves out as trained and experienced in given areas, and that such a standard is routinely applied in the medical field. *Id.* The court added, "we can expect abortion clinics to consult relevant legislation in advance of action or to seek clarification from appropriate administrative sources when necessary." *Id.* at 367.

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[7] *See also Karlin*, 188 F.3d at 464-68 (finding that an informed consent regulation provided "fair warning" to physicians and "fair enforcement" by authorities in part because physicians are accustomed to having their medical decisions judged under an objective standard).

Finally, in *Fargo Women's Health Organization v. Schafer*, the Eighth Circuit analyzed the term "medical emergency" in a South Dakota informed consent statute. 18 F.3d 526 (8th Cir. 1994). The court explained that, when the phrase "medical emergency" was viewed in light of the purpose section of the act, it was clear that the state intended to protect maternal health. *Id.* at 535. The court's "common sense interpretation" of the statute "easily" led it to conclude that physicians were fully capable of understanding the statute's requirements. *Id.*[8]

B. The common sense interpretation of "federal law" includes the 49-day gestational limit in the FDA approval letter and the treatment protocols and dosage indications described in the drug's final printed labeling

Under the guidance of the aforementioned Ohio and federal court jurisprudence, the "common sense interpretation" of "federal law" is clear. *See Fargo*, 18 F.3d at 535. All that is asked of the legislature is that persons of ordinary intelligence—and in this case, physicians of ordinary intelligence—be able to ascertain what is meant by "federal law." *See, e.g., Founder's Women's Health Center*, 2002 Ohio App. LEXIS 4345, *33. Moreover, this ordinary intelligence must be taken in context with the whole of the physicians' highly trained medical practice, including those tasks which physicians perform routinely. *See, e.g., Vuitch*, 402 U.S. at 72; *Bolton*, 410 U.S. at 192; *Karlin*, 188 F.3d at 464-65, 477; *Greenville Women's Clinic*, 317 F.3d at 366. Thus, "federal law" is to be assigned that commonsense meaning which would be generally understood by these highly trained professionals and used routinely in their practices.

As defined in the statute, "federal law" means "any law, rule, or regulation of the United States or any drug approval letter of the food and drug administration of the United States that governs or regulates the use of RU-486 (mifepristone) for the purpose of inducing abortions."

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[8] *See also Planned Parenthood of Minn./S.D. v. Rounds*, 372 F.3d 969, 974 (8th Cir. 2004) ("When both sides agree to the meaning of a particular word, we do not see how either side can say, in good faith, that it was unable to understand the meaning of that word.").

OHIO REV. CODE § 2919.123(F)(1). As this Court is well aware, the Respondents claim that it is unclear "whether the Act's inclusion of the FDA approval letter in the definition of federal law renders it illegal for a physician to prescribe" the protocol they prefer to prescribe. *See Planned Parenthood Cincinnati Region v. Taft*, 459 F. Supp. 2d 626, 631 (S.D. Ohio 2006). Specifically, Respondents claim it is unclear whether "federal law" includes the 49-gestational limit in the FDA approval letter and the protocol delineated in the mifepristone label.

First, the common sense interpretation of "federal law"—which unambiguously includes "any drug approval letter" of the FDA—includes the 49-day gestational limit in that FDA approval letter. To claim otherwise is contrary to any person's common sense interpretation of the law.

Moreover, the mifepristone label[9] accompanying the drug explains in unambiguous words that it "is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy."[10] Under the heading "Dosage and Administration," the label explains that treatment requires three office visits by the patient and may only be administered in a clinic, medical office, or hospital under the supervision of a physician. The label then states that on Day One, three 200 mg tablets are taken in a single oral dose; on Day Three, the patient returns and, unless an abortion has occurred and is confirmed, the patient takes two more tablets orally. The label also provides that on Day 14, the patient is to return for a follow-up visit in order to confirm that

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[9] The federal district court refers to this label as the "final printed labeling instructions," or "FPL." *See Taft*, 459 F. Supp. 2d at 635.

[10] *MIFEPREX™ (mifepristone) Tablets, 200 mg For Oral Administration Only* (mifepristone label), at: http://www.fda.gov/Cder/foi/label/2000/20687lbl.htm (last visited Sept. 26, 2008). This label is easily accessible on the FDA's website.

a complete termination has occurred. In addition, the label's title states "for oral administration only."

The Respondents are not "confused" by the FDA's protocol. Even the federal district court explicitly stated that the FDA protocol "that the FDA tested and on which it based its approval of mifepristone consisted of three oral doses of 200 mg of mifepristone followed by a single dose of .4 mg misopristol also taken orally, through 49 days LMP." *Id.* at 630 n.7. Thus, the Respondents are not confused with regard to the exact protocol outlined by the FDA. *See Rounds*, 372 F.3d at 974 (stating that when both sides agree to a meaning of a word, neither side can argue it is vague). Instead, the Respondents only argue that it is unclear whether the Act includes the FDA protocol, including the 49-day gestational limit and dosage and administration instructions in the label, in its definition of "federal law." As is demonstrated below, the Respondents are merely grabbing at straws in order to defend their preferred—and untested and unapproved—protocol.

Physicians are called upon on a daily basis to provide prescriptions for a variety of medications. Likewise, physicians routinely provide those prescriptions in accordance with federal guidance and FDA-approved labeling. It is not confusing that FDA protocol and labeling for any drug would be included in a definition of federal law. The "routineness" of a practice is constantly cited in decisions upholding challenged abortion laws. *See Bolton*, 410 U.S. at 192; *Vuitch*, 402 U.S. at 72; *Greenville Women's Clinic*, 317 F.3d at 366; *Karlin*, 188 F.3d at 464-65. In the same way, "federal law" includes the mifepristone label, because the routine nature of consulting drug labels negates any claims to the contrary.

Furthermore, § 2919.123 is to be examined in light of the ordinary person's reading of the Act. Here, the "ordinary person" is a physician, called upon routinely to prescribe

medications in accordance with FDA guidelines. As noted in *Greenville Women's Clinic*, we can expect a physician to consult relevant legislation and FDA protocol in advance of an action, or to seek clarification from appropriate administrative sources when necessary. *See Greenville Women's Clinic*, 317 F.3d at 367. Physicians are intelligent and highly trained and should have no difficulty complying with § 2919.123 after a "minimum amount of diligence." *See Karlin*, 188 F.3d at 477.

Even if physicians routinely fail to follow the protocol outlined in FDA-approved labels, the provisions of § 2919.123 itself provide guidance as to what is included in "federal law." Section 2919.123(B) provides that no physician "shall knowingly fail to comply with the applicable requirements of any federal law *that pertain to follow-up examinations*...." OHIO REV. CODE § 2919.123(B) (emphasis added). As demonstrated above, the mifepristone label unambiguously pertains to follow-up care. Thus, when taken "as a whole,"[11] the text of § 2919.123 points to the mifepristone label, which clearly sets forth the required FDA protocol.

In examining the whole of the law, it is also important to note that the law is aimed at the protection of women. *See* Part II., *infra*. Because of its protective purpose, the law "operates for the benefit, not the disadvantage," of women. *Bolton*, 410 U.S. at 192. Likewise, in order for this court to interpret the subject provisions in light of the statute's intent, those provisions should be interpreted for the protection of women. Here, it is clear that mifepristone was only tested and approved through 49 days gestation, and only in accordance with the protocol outlined in the drug's label. This Court should give deference to the legislature's intent in protecting women, and interpret the phrase "federal law" to include the protocol that will be most protective of women. Defining "federal law" to include the 49-day gestational limit in the FDA approval

[11] *See Grayned*, 408 U.S. at 110; *Greenville Women's Clinic*, 317 F.3d at 366.

letter and the protocol outlined in the mifepristone label simply "operates for the benefit, not the disadvantage, of the pregnant woman." *Id.*

In summary, this is not a case where an ordinary citizen is called upon to understand that he or she must comply with federal law. This is a case where highly-trained physicians are instructed to comply with federal law in prescribing and dispensing a medication. This is an action undertaken routinely by physicians, and physicians routinely check and abide by protocols approved in FDA letters and drug labels. The statute itself defines "federal law" to include drug approval letters, and the drug approval letter includes the 49-day gestational limit. Moreover, the statute states that physicians must comply with any federal law that pertains to follow-up care, and the mifepristone label clearly pertains to follow up care. And finally, in order for this Court to honor the legislature's intent in protecting women under this statute, this Court should interpret "federal law" to include those provisions which will best protect women against the dangerous off-label effects of mifepristone. *See* Part II, *infra*. For each of these reasons, "federal law" must be interpreted to include the 49-day gestational limit in the FDA approval letter as well as the protocol clearly delineated in the mifepristone label.

Proposition of Law No. II: The severe medical risks inherent in the use of mifepristone and its off-label use underscore the necessity of including the FDA approval letter and the mifepristone label in the definition of "federal law"

OHIO REV. CODE § 2919.123 was enacted for the protection of women. As detailed below, even when physicians and patients abide by the federal protocol outlined in the FDA's approval letter and the drug's label, use of mifepristone poses significant risks for women. And as this Court is fully aware, the United States Supreme Court has affirmed time and time again that states have significant—even compelling—interests in protecting women from the harms and risks of abortion.

To date, at least eight American women have died from mifepristone abortions. The dangerous risks of mifepristone demand strict adherence to the FDA-approved protocol. Off-label use of mifepristone is deadly, and the necessity of § 2919.123—and Ohio's compelling interest—is obvious.

The medical evidence examined below, along with the discussion presented in the Appendix, demonstrates that the federal protocol—including the 49-day gestational limit in the FDA approval letter and the treatment protocols and dosage indications in the drug's label—makes sense medically and serves to protect women's health and establish a uniform standard for the administration of mifepristone. Section 2919.123 is thus directly and strongly related to protecting women's health by requiring that Ohio providers follow the standard of care in the federal protocol.

A. The use of mifepristone presents significant medical risks to women

1. Death by *C. sordellii* bacterial infection

From September 2003 through June 2005, the FDA reported four U.S. deaths due to *C. sordellii* bacterial infection in women, ages 18-34, who had undergone mifepristone abortions.[12] All four patients were two months pregnant and received the off-label dosages and vaginal administration preferred by the Respondents. All died within five to seven days following receipt of mifepristone, with identical clinical signs of shock, absence of fever, increase in leukocytes and red blood cells, and decrease in plasma volume. The time from hospital

[12] *Sepsis and Medical Abortion*, at: http://www.fda.gov/cder/drug/advisory/mifeprex.htm (last visited Sept. 26, 2008); *Emerging Clostridial Disease Workshop* (CDC-FDA-NIH Transcript May 11, 2006), at: http://www.fda.gov/cder/meeting/clostridia_disease.htm (last visited Sept. 26, 2008) (CDC Workshop).

admission to death was a matter of hours, and one woman collapsed and died before reaching the hospital.[13]

These deaths demonstrated that severe infection occurs unpredictably, is difficult to identify, and is difficult to treat due to the absence of usual symptoms of infection (*e.g.*, fever). Once identified, it can result in death in a matter of hours.[14]

Multiple species of *Clostridium*, including *sordellii* (*C. sordellii*), are found in 8-18 percent of all women.[15] Yet *C. sordellii* is usually suppressed by a normally functioning immune system, and therefore infection in healthy, young women is very rare and "occurs primarily among patients with serious underlying immunoconditions."[16] However, these four U.S. women were reported by the Centers for Disease Control (CDC) and FDA as having been previously healthy, without any underlying immunoconditions.[17] They had no risk factors predisposing

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[13] Fischer et al., *Fatal Toxic Shock Syndrome Associated with Clostridium sordellii after Medical Abortion*, N.E. J. MED. 353:2352-60 (2005); CDC Workshop, *supra*, at 79-82, 104-105; Gary & Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, ANNALS OF PHARM. (Feb. 2006).

[14] Miech, *Patholphysicology of Mifepristone-Induced Septic Shock Due to Clostridium sordellii*, ANNALS OF PHARM. (Sept. 2005); Statement by Donna Harrison, M.D., for *RU-486: Demonstrating a Low Standard for Women's Health?*, Hearing before the Committee on Government Reform, House of Representatives (May 17, 2006), Serial No. 109-202, at: http://www.gpoaccess.gov/congress/index.html (last visited Sept. 26, 2008); Fischer, *supra*, at 2356, 2358; Gary-Harrison, *supra*.

[15] Fischer, *supra*, at 2358; CDC Workshop, *supra*, at 93, 107.

[16] CDC Workshop, *supra*, at 76-77, 93, 115; Meich, *supra*, at 1484; Harrison, *supra*, at 139; Calhoun & Harrison, *Challenges to the FDA Approval of Mifepristone*, ANNALS OF PHARM. 166 (Jan. 2004); Fischer, *supra*, at 2356.

[17] Fischer, *supra*, at 2352-53, 2356; CDC Workshop, *supra*, at 79; Harrison, *supra*, at 139.

them to infection or death—especially from a bacterium that rarely affects humans with a normal immune system.[18]

Medical literature explains that this phenomenon occurs because mifepristone can prevent the proper functioning of the immune system and cause fatal toxic shock.[19] Mifepristone blocks receptors that play a necessary role in the immune system's response to bacteria. Combined with the mifepristone effects of a softened, open cervix and lack of protective mucous, this impairment of the immune system allows *C. sordellii* to enter the uterus and multiply. Once established in the uterus, it secretes lethal toxins, which break down G-proteins, the molecular switches that activate the functions necessary for cellular immune responses.[20]

In addition, mifepristone blocks the hypothalamic-pituitary-adrenal (HPA) axis, which controls an essential aspect of the body's immune system. When the proper functioning of the HPA axis is prevented, dangerous levels of excess cytokines, or proteins, are released.[21] The combined entrance of excess cytokines and lethal toxins into the circulatory system causes toxic shock syndrome, multiple organ failure, and, ultimately, death.[22] This causal chain between mifepristone and death by toxic shock syndrome has been demonstrated in multiple animal

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[18] Harrison, *supra*, at 135.

[19] Webster & Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glococorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, J. ENDOCRIN. 181, 207-21 (2004); Miech, *supra*; Gary-Harrison, *supra*; Harrison, *supra*; CDC Workshop, *supra*, at 76-121.

[20] Miech, *supra*, at 1484; CDC Workshop, *supra*, at 109.

[21] McGregor, *Response to letter to the editor*, CONTRACEPTION 74, 174-77 (2006).

[22] CDC Workshop, *supra*, at 108-10, 115, 118; Miech, *supra*; Gary-Harrison, *supra*; Webster-Sternberg, *supra*.

models of septic shock,[23] ***where the mortality rate increased from 13 percent to 100 percent in mifepristone-treated animals.***[24]

In the deaths of the four U.S. women, the symptoms appeared four to five days after receipt of mifepristone.[25] While most drugs are metabolized and eliminated from the body in a few hours, mifepristone has an unusually long half-life of 30 hours. It thus takes four to five days to remove 95 percent of mifepristone from the body, and in some women, it can take up to 18 days.

Furthermore, because mifepristone abortions typically involve severe cramping, women are frequently prescribed codeine. Codeine competes with mifepristone for the enzyme that breaks down mifepristone, thereby prolonging the drug's lengthy presence in the uterus. *C. sordellii* then has enough time to establish itself, multiply, and secrete lethal, immunity-impairing toxins, contributing to the onset of fatal toxic shock.[26]

Medical scholarship, scientific data, and cases of recent fatalities in the U.S. support the conclusion that abortion by mifepristone presents a significant risk of death.[27] In short, mifepristone's anti-progesterone mechanism makes the uterus "a fertile medium of dead fetal tissue surrounded by an endometrium that lacks normal innate immune responses"[28] and an

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[23] CDC Workshop, *supra*, at 91, 108, 115.

[24] Sternberg, *Proceedings of the Nat'l Acad. Sci.* 86: 2374-78 (1989); Harrison, *supra*, at 135, 138.

[25] Fischer, *supra*, at 2352-53.

[26] CDC Workshop, *supra*, at 79, 89, 105-06.

[27] Letter from Donna Harrison, M.D., to Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy and Human Resources, at Q.1(b) (Souder letter); Harrison, *supra*, at 138-39.

[28] Gary-Harrison, *supra*, at 109.

"ideal bacterial culture for *C. sordellii*."[29] Mifepristone's blockage of the HPA axis, combined with exposure to *C. sordellii*, places women in a vulnerable state. The blockage of glucocorticoid receptors prohibits the body from protecting itself from the lethal toxins and excess cytokines. As a result, the body undergoes fatal toxic shock.

2. Other life-threatening infections

Through July 2005, the FDA reported at least 46 cases of life-threatening infections requiring hospitalization. Reported cases included septic shock, toxic shock syndrome, adult respiratory distress syndrome from sepsis, *Escheria coli* sepsis, group B Streptococcus septicemia, disseminated intravascular coagulopathy (DIC) with heptic and renal failure, and severe pelvic infection. Four of these cases required ICU hospitalization. An additional 14 patients were treated for pelvic infections as outpatients. Severe pelvic infection also presents an increased risk of subsequent ectopic pregnancy, tubal occlusion with subsequent infertility, and chronic pelvic pain from adhesive disease.[30]

3. Massive hemorrhage

The FDA has reported that at least 116 women have required blood transfusions for massive bleeding after mifepristone abortions, with at least 54 losing over one-half of their blood volume. These women would have died without immediate access to sophisticated emergency facilities equipped to perform large blood transfusions. Medical research has shown that one to two of every 1,000 women who undergo mifepristone abortions will require emergency blood

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[29] CDC Workshop, *supra*, at 109.

[30] Gary-Harrison, *supra*, at 192-93; Harrison, *supra*, at 141; Medwatch Adverse Event Reports, *Individual Safety Report nos. 3803789-5, 4327968-6, 4411599-3, 4199811-X, 3915940-9, & 3943786-2* (FDA Office of Postmarking Drug Risk Assessment).

transfusion for massive hemorrhage. Because no risk factors have been identified, it is impossible to predict or prevent massive hemorrhage from mifepristone abortion.[31]

4. Further dangers specifically associated with off-label use

Ectopic pregnancy is an absolute contraindication to mifepristone,[32] and the only way it can be discovered is by ultrasound.[33] Because symptoms of ectopic pregnancy mimic the symptoms of completed mifepristone abortions, ectopic pregnancies go easily undiagnosed.[34]

Improper screening and failure to follow FDA protocol requiring follow-up care place the lives of women with unknown ectopic pregnancies at even greater risk of death by ruptured ectopic pregnancy. The FDA has reported that at least 17 women have had undetected ectopic pregnancies during mifepristone administration, eleven of which resulted in ectopic rupture. One of these eleven women bled to death—a death which would not have occurred if the ectopic pregnancy had been properly diagnosed.[35] The absence of ultrasound use and follow-up care also increases the risk of retained tissue, thereby increasing the risk of infection.[36]

In addition, disregard for mifepristone's failure rate increases medical risk. It is generally understood that the percentage of incomplete mifepristone abortions requiring emergency surgical intervention increases with gestational age. Mifepristone's failure rate is 8 percent at 49

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[31] Harrison, *supra*, at 136, 141-42; Gary-Harrison, *supra*, at 192; Paul et al., *A Clinician's Guide to Medical and Surgical Abortion* 202 (1999).

[32] Gary-Harrison, *supra*, at 195.

[33] Calhoun-Harrison, *supra*, at 165.

[34] Medical Management of Abortion, *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician Gynecologists* 26(4):1-20 (2001); Calhoun-Harrison, *supra*, at 165.

[35] Gary-Harrison, *supra*, at 192-93; Medwatch, *supra*, *Individual Safety Report no. 3806144-7.*

[36] Calhoun-Harrison, *supra*, at 165.

days gestation, 17 percent at 50-56 days gestation, and 23 percent at 57-63 days gestation. Abdominal pain, nausea, diarrhea, and vaginal bleeding also increase with increasing gestational age.[37] Despite these known statistics, the Respondents continue to advocate use of mifepristone past the FDA's 49-day protocol.

B. Mifepristone offers no net therapeutic benefits over the safer alternatives

1. Risk of death from *C. sordellii* bacterial infection elevated in mifepristone use

In 30 years, there have been no reported deaths from *C. sordellii* following surgical abortion. At less than eight weeks gestation, it has been reported that the rate of death from infection by all causes, except *C. sordellii*, is 0.1 per 100,000 surgical abortions, which means that the risk of death from *C. sordellii* after a mifepristone abortion is at the very least ten times the risk of death from all other types of bacterial infection in surgical abortion procedures.[38] In addition, the risk of death from *C. sordellii* after mifepristone abortion is ***fifty times the risk of death*** from *C. sordellii* after surgical abortion.[39]

2. Risk of hemorrhage elevated in mifepristone use

The risk of hemorrhage from mifepristone is much greater than the risk of hemorrhage from surgical abortion.[40] A study specifically comparing the outcomes of surgical and mifepristone abortions found that, of the women who required surgery to complete an abortion after receiving mifepristone, 12.5 percent also underwent emergency surgery for acute bleeding.

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[37] Calhoun-Harrison, *supra*, at 165; Spitz et al., *Early Pregnancy Termination with Mifepristone and Misoprostol in the United States*, N.E. J. MED. 338:1241-47 (1998).

[38] Calhoun-Harrison, *supra*, at 165; Greene, *Fatal Infections Associated with Mifepristone-Induced Abortion*, N.E. J. MED. 353; 22 (Dec. 1, 2005).

[39] Harrison, *supra*, at 135, 141; Fisher, *supra*, at 2358; Souder Letter, *supra*, at Q.1(b).

[40] Harrison, *supra*, at 136, 142-44; Souder Letter, *supra*, at Q.1(b), 2, 5, 7.

In contrast, no women in the surgical abortion group required emergency surgery for acute bleeding.[41]

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Statistics demonstrate that both surgical abortion and childbirth are safer alternatives to mifepristone abortion. One scientific study has also revealed that mifepristone abortions fail more often than surgical abortion, have more subsequent bleeding for a longer duration of time, require more emergency surgical intervention, and are more painful than surgical abortions.[42] Thus, mifepristone does not offer women any net therapeutic benefit; rather, it exposes women to greater medical risk.

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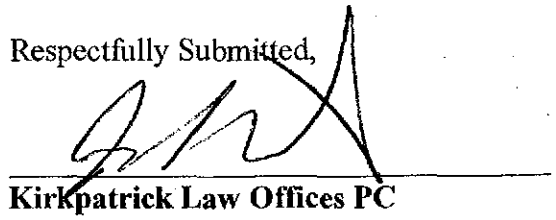
[41] Jensen et. al, *Outcomes of Suction Curettage and Mifepristone Abortions in the United States: A Prospective Comparison Study*, CONTRACEPTION 59-153-59 (1999).

[42] *Id.;* Souder Letter, *supra*, at Q.5.

CONCLUSION

Amici urge this court to answer both certified questions in the affirmative.

Respectfully Submitted,



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APPENDIX

UNITED STATES HOUSE OF REPRESENTATIVES
GOVERNMENT REFORM COMMITTEE

OCTOBER 2006

THE FDA AND RU-486: LOWERING THE STANDARD FOR WOMEN'S HEALTH

STAFF REPORT

PREPARED FOR THE HON. MARK SOUDER
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I. EXECUTIVE SUMMARY

This report explores the Food and Drug Administration's activities as they relate to RU-486 – the abortion pill – including the highly unusual process by which the drug was approved, the failures to ensure that the drug is dispensed as the Food and Drug Administration (FDA) requires, the subsequent illnesses, hospitalizations and deaths known to be associated with the drug and the failure to provide any meaningful restrictions despite evidence of its association with a 100% fatal septic infection.

On May 17, 2006, Congressman Mark Souder, Chairman of the Subcommittee on Criminal Justice, Drug Policy and Human Resources ("Subcommittee"), House Committee on Government Reform, convened a hearing to inquire into the safety of the FDA-approved drug Mifeprex (the trade name for mifepristone) commonly known as RU-486. The hearing was entitled, "RU-486 - Demonstrating a Low Standard for Women's Health?" The Subcommittee's hearing followed several months of investigative inquiries with the FDA after the Agency's July 2005 disclosure that four women had died of a septic infection after taking RU-486 to induce an abortion.[1]

This Subcommittee Staff Report ("Report") provides background information about RU-486, including the reasons the drug was brought to market. It also explores the allegation that FDA disregarded various statutes and rules in the RU-486 approval process, and it examines RU-486's safety record in the United States. The accumulation of safety data from "real world" use of the drug in America has allowed Subcommittee investigators to more completely grasp FDA's understanding of the risks posed by RU-486 when it approved the drug on September 28, 2000.

Based on the significant demonstrated danger this drug poses to women, the Report examines options for withdrawing this drug from the market.

II. BACKGROUND

RU-486 is the common name for mifepristone, which in the United States is marketed under the trade name Mifeprex. Shanghai HuaLian Pharmaceutical Co., Ltd.[2] of China produces the drug, which is imported and distributed by Danco Laboratories,[3] a corporate entity located in the Caribbean nation of the Cayman Islands. RU-486, Danco's sole product,[4] is approved for the

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[1] FDA Public Health Advisory: Sepsis and Medical Abortion, July 19, 2005. Available at http://www.fda.gov/cder/drug/advisory/mifeprex.htm (last visited October 14, 2006).

[2] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Senator Jim DeMint (August 11, 2006) (on file with Subcommittee).

[3] *See, Foes criticize Chinese manufacture of abortion pill for U.S.*, CNN.com, (Oct. 13, 2000) at http://archives.cnn.com/2000/HEALTH/women/10/13/abortionpill.plant.ap/index.html (last visited October 10, 2006).

[4] Unlike other drug companies with multiple products that are approved by or in application before the FDA--and which therefore cooperate with the FDA to withdraw drug products when recognizable problems arise--Danco has

termination of an established pregnancy through 49 days development (LMP),[5] when used in conjunction with the prostaglandin, misoprostol.[6]

RU-486 terminates pregnancy by blocking progesterone receptors in the uterus, a hormone necessary for the maintenance of pregnancy.[7] This leads to degeneration of the uterine lining, blocking nutrition to the prenate, thus resulting in its death.[8] Mifeprex is used in combination with a prostaglandin called misoprostol, which causes contractions that expel the contents of the uterus.[9] This is an off-label use for misoprostol, which contains an FDA-mandated black-box warning against using the drug during pregnancy.[10]

Under the protocol approved by the FDA – one considerably less stringent than the agency's proposed protocol leaked to the public a few months prior to approval – if the patient is

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no other products for which it must be answerable to the FDA. *See also,* Rogoff, Natasha L, *Haven or Havoc?,* PBS Frontline, February 19, 2004 at http://www.pbs.org/wgbh/pages/frontline/shows/tax/schemes/cayman.html.

[5] FDA Approval Memo (September 28, 2000); "LMP" refers to the first day of the last menstrual period, and is the customary measure of gestational age, from approximately 14 days pre-fertilization of the conceptus.

[6] The FDA examined misoprostol to see if the deadly *Clostridium Sordellii* bacteria that killed four California women after taking RU-486 was associated with misoprostol, rather than the Mifeprex: "An FDA Public Health Advisory in mifepristone dated July 22, 2005 reported 4 cases of septic death in California following the use of mifepristone and intravaginal misoprostol for medical abortion. For this reason, DRUP [Division of Reproductive and Urologic Products] and DDRE [Division of Drug Risk Evaluation] met on July 19, 2005, to discuss searches of the AWRS database to further investigate this cluster of repo0rts. At this meeting, DDRE agreed to provide 3 consults to examine this issue... The proposed consults were as follows:

- Consult #1: Review of all reports of serious infections with misoprostol in women of childbearing age
- Consult #2: Review of all reports for suspected intravaginal products with a fatal outcome
- Consult #3: Review of all serious, unusual infections with intravaginal products."

"This review did not identify any new safety signal associated with intravaginal product administration, especially in regards to infection or pregnancy status." FDA Office of Drug Safety Postmarketing Safety Review, December 8, 2005 (on file with the Subcommittee).

The FDA also tested the manufacturing lots from which the misoprostol was distributed and eliminated that drug product as a source of contamination that would have caused the fatal *C. Sordellii* infections. *See* Marc Fischer, M.D., M.P.H., CDC, *Clostridium sordelli Toxic Shock Syndrome Following Medical Abortion*, Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Available at http://www.fda.gov/cder/meeting/clostridial/fisher.pdf (last visited October 20, 2006).

[7] See., e.g., University of Chicago Department of Obstetrics and Gynecology, Information on Hormonal Imbalance, available at http://babies.bsd.uchicago.edu/endo/hormoneImbalance.htm (last visited October 10, 2006).

[8] Etienne-Emile Baulieu, "RU-486 as an Antiprogesterone Steroid: From Receptor to Contragestion and Beyond," *Journal of the American Medical Assn.* 262:13; 1808-1814 (October 6, 1989).

[9] Pfizer (along with their generic subsidiary) and Teva Pharmaceuticals, the makers of misoprostol, have never filed a New Drug Application to seek approval from the FDA for its use in abortion. It was approved for use with ulcers, and is contraindicated for pregnancy. Pfizer's German affiliate recently pulled the drug from the market.

[10] Cytotec (misoprostol) Full Revised Label, April 17, 2002, available at www.fda.gov/cder/foi/label/2002/19268slr037.pdf (last visited October 10, 2006).

found to be a candidate for a chemical abortion (according to criteria such as gestational age of 49 days or less, absence of ectopic pregnancy and a host of health contraindications), she is given 600 mg of Mifeprex to consume at once and instructed to return two days later to consume orally 400 mcg of misoprostol. Patients are further instructed to return in 14 days for a follow-up, which could include a surgical abortion in the three percent to 7.9% of cases in which the chemical abortion fails.[11]

Many providers, however, deviate from the FDA protocol, extending the RU-486 abortion cut-off to 56 and even 63 days' gestation,[12] cutting the dose of Mifeprex by two-thirds, and handing the patient misoprostol pills to insert vaginally at home two days later.[13] Failure rates at these gestational ages are approximately 17% and 23% respectively.

In the decade preceding FDA approval of RU-486 for use in the United States, advocates of RU-486 promoted the drug as a private, easy, safe and effective method of pregnancy termination,[14] offering women the choice of ending pregnancy at an earlier stage and in a less "invasive," instrumented manner, when compared to surgical and suction abortion methods.[15] In sum, the public was told that access to RU-486 had everything to do with women's privacy and choices.

Cited as justification for RU-486 approval and use were the following goals: "defusing the abortion conflict,"[16] putting abortion "into the medical mainstream and out of this ghettoized place it's been in,"[17] making "abortion ... more socially acceptable,"[18] "expanding the number

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[11] See Mifeprex Label ("Medical abortion failures should be managed with surgical termination." Also, "Each patient must understand...that medical abortion treatment failures are managed by surgical termination.") at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited October 10, 2006).

[12] Some abortion providers (e.g., Planned Parenthood of New York City at www.ppnyc.org/services/factsheets/mifep.htm, Capital Care Women's Center at www.capitalcarewomenscenter.com/services.php, and Camelback Family Planning at www.camelbackfamilyplanning.com/abortionpill.html.), even advertise the availability of RU-486 through 63 days LMP, by which time the rate of incomplete abortion, infection, and other complications rises sharply. In U.S. clinical trials, the failure rate for RU-486 abortions jumps to 17% at 50-56 days LMP, and to 23% at 57-63 days LMP, from 8% at 49 days or less. Irving Spitz *et al.*, "Early pregnancy termination with mifepristone and misoprostol in the United States," *New England Journal of Medicine* 1998, 338:1241-47.

[13] Evidence of this method deviation can be found in many Adverse Event Reports, including those reporting on the deaths of four California women from toxic shock related to *C. Sordellii.*

[14] Lawrence Lader. RU486: The Pill that Could End the Abortion Wars and Why American Women Don't Have It. Reading, Mass.: Addison-Wesley Publ. Co., 1991, 17-26.

[15] Planned Parenthood of New York City Press Release, December 4, 2000: "Women will now have access to this option of a very safe, early abortion without undergoing an invasive procedure. ... By allowing women to take part in their own care, mifepristone offers women more privacy in their decisions and control over their bodies."

[16] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Seattle abortion provider Suzanne Poppema, M.D.

[17] *Ibid*, quoting Carole Joffe, professor of sociology, University of California-Davis.

[18] *Ibid.*

of abortion providers"[19] and even advancing the U.S. aim of "population control"[20] in the developing world. One vocal advocate explained: "Abortion in the U.S. is this degraded, shameful, violence-surrounded thing. ...It's not like that in Europe. So that makes our context for medical [e.g., RU-486] abortion unique."[21] Safety and efficacy questions were brushed aside with assurances that several hundred thousand women in France and China had already used RU-486 to induce abortion.[22]

One might reasonably wonder why, when the surgical option is readily available and exponentially safer,[23] the FDA would approve, or the abortion industry would support, a chemical procedure that subjects women to increased pain and risk. To answer this question, it is helpful to understand abortion industry fears concerning the dwindling number of providers, and to assess the industry's leverage and access within the FDA.

The National Abortion Federation reported in May 2004 that the "number of abortion providers has declined by 37% since 1982."[24] In 1997, 36% of ob/gyns reported ever performing elective abortions.[25] Among them, 57% were fifty years of age or older and another 30% were 40 or older.[26] In other words, the abortion industry perceived that—unless drastic measures were taken—it was in danger of losing nearly 57% of its doctors by 2012 and 87% of its doctors by 2022, significantly reducing the availability of abortion in the United States.[27]

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[19] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Seattle abortion provider Suzanne Poppema, M.D.

[20] Nathanson, Bernard, "Drugs for the Production of Abortion: A Review," Obstet & Gyn Survey 25:8; 727-731 (1970); Renate Klein *et al.*, RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 59: "It is a further misconception to believe that this [RU-486] research took place in order to expand or improve women's 'choices' to control their reproduction. Quite unmistakenly, the concept evolved as a means of population control. More than 20 years ago, the Center of Population Research of the U.S. National Institutes of Health became interested in the corpus luteum and called for research to determine whether to find 'means to inhibit corpus luteum function is a desirable goal'. The specific intention of such research was to restrict population growth in countries that were judged to be 'under-developed.' If successful, the method(s) could be extended to groups in the United States, Black, Hispanic and Native American Women (Department of Health, Education and Welfare, NIH, USA, 1969)."

[21] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Carole Joffe, professor of sociology, University of California-Davis.

[22] Lawrence Lader. A Private Matter: RU-486 and the Abortion Crisis. Amherst, N.Y.: Prometheus Books, 1995, 115-117.

[23] The Alan Guttmacher Institute, an affiliate of Planned Parenthood, reports that the mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318.

[24] Abortion Access Project, Fact Sheet: The Shortage of Abortion Providers, May 6, 2004, available at www.abortionaccess.org/AAP/publica_resources/fact_sheets/shortage_provider.htm (last visited October 10, 2006).

[25] Kaiser Family Foundation, *Abortion*, Issue update, Menlo Park, CA: Kaiser Family Foundation, May 1999.

[26] *Ibid.*

[27] Lawrence B. Finer and Stanley K. Henshaw, "Abortion Incidence and Services In the United States in 2000," Perspectives on Sexual and Reproductive Health, 2003, 35(1):6-15.

The industry, then, out of concern for its own preservation, pinned its hopes on chemical abortion. A Kaiser Family Foundation survey, for example, noted: "Many reproductive health groups in the U.S. have looked to widespread availability and marketing of mifepristone ... to expand access to abortion in this country."[28] Pediatrician Eric Schaff, who oversaw at least one RU-486 trial, put the matter somewhat more crudely. Objecting to an FDA proposal (never formally adopted) that any doctor dispensing RU-486 would have to be trained in surgical abortion, Dr. Schaff explained, "The whole idea of [RU-486] was to increase access. ... [The FDA proposal] kills the drug if it can't be used by primary care providers."[29]

Despite the problems associated with RU-486 (discussed in depth in Section III, below), it looked like a panacea for the abortion industry. Advocates predicted that the number of providers would increase. The Kaiser Family Foundation stated that one-third of all ob/gyns who did not perform abortions said they would be "very" or "somewhat" likely to prescribe mifepristone for abortions if approved by the FDA.[30] Furthermore, rather than limiting abortion procedures to medical doctors alone, advocates saw an opportunity for nurse practitioners, nurses, and others to administer abortions to women.[31]

In June 1989, one year after its introduction into the French market, the FDA issued an import alert on RU-486. The concern was that women would obtain the drug themselves and use it without support from a physician. The wisdom of this policy is supported by the fact that, as the RU-486 label states, nearly *all* users of RU-486 will experience adverse events.[32] But it wasn't long before Democrats, led by then-Representative Ron Wyden of Oregon, seized this opportunity to politicize the approval process.

Under the auspices of the Committee on Small Business's Subcommittee on Regulation, Business Opportunities and Energy, as early as September 18, 1990, Representative Wyden was investigating the FDA's import alert on RU-486, alleging that the FDA's overriding concerns for the alert were political, rather than medical, and that the actions of the FDA were preventing cures for several diseases, including breast and brain cancer, Cushing's disease, glaucoma and

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[28] Kaiser Family Foundation, News Release, June 8, 2000, available at www.kff.org/womenshealth/20000613a-PressRelease2.cfm (last visited October 10, 2006).

[29] Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times*, June 8, 2000.

[30] Kaiser Family Foundation, News Release, June 8, 2000, available at www.kff.org/womenshealth/20000613a-PressRelease2.cfm (last visited October 10, 2006).

[31] Press release, Ibis Reproductive Health, the National Abortion Federation, and the Abortion Access Project, May 9, 2006, available at www.prochoice.org/news/releases/20060509.html (last visited October 10, 2006).

[32] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006): "Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction."

diabetes. Two hearings in his committee followed, one in November of 1990[33] and another in December, 1991.[34]

Following these hearings, Representative Wyden introduced legislation to prohibit the FDA from taking any action to bar the import of RU-486 unless the FDA finds that it is being imported for an illegal use.[35]

It is interesting to contrast the interests of Representative Wyden and the abortion industry with the concerns of the American Medical Association (AMA), which offered this view about the health and safety of women who might obtain and use RU-486 without a physician's supervision:

> "[I]t is the AMA's understanding that RU-486 poses a severe risk to patients unless the drug is administered as part of a complete treatment plan under the supervision of a physician...Rumors exist that the FDA, due to political pressure, is standing in the way of research on RU-486. We do not believe this to be true. On the contrary, it is the FDA's responsibility to ban a drug that has not met legal and regulatory requirements for importation into the United States. Because RU-486 has not met these requirements, the FDA complied with its charge and acted well within its authority in issuing its June 9, 1989, automatic detention import alert concerning the drug."[36]

In the meantime, women's groups orchestrated an offensive consisting of media stunts to exert political pressure on the FDA. Lawrence Lader, founding chairman of the then-National Abortion Rights Action League (NARAL), and Ms. Leona Benton, who volunteered to serve as a "test case," traveled to Europe to acquire RU-486 with the specific purpose of being apprehended by Customs agents when they returned on July 1, 1992.[37] Agents seized the pills, and 45 members of the press showed up to publicize her "plight."

Ms. Benton immediately filed suit against the FDA in federal district court (Brooklyn), and Judge Charles Sifton ruled in her favor on July 14. Before she could physically recover the confiscated pills, however, government attorneys filed an appeal with the U.S. Court of Appeals for the Second Circuit, where a three-judge panel reversed Judge Sifton's order. The U.S. Supreme Court accepted an expedited appeal and, on July 17, ruled 7-2 against releasing the

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[33] *RU-486: The Import Ban and its Effect on Medical Research: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Nov. 19, 1990).

[34] *Safety and Effectiveness of the Abortifacient RU-486 in Foreign Markets: Opportunities and Obstacles to U.S. Commercialization: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Dec. 5, 1991).

[35] H.R. 875 "RU-486 Regulatory Fairness Act of 1991," introduced February 6, 1991.

[36] *RU-486: The Import Ban and its Effect on Medical Research: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Nov. 19, 1990) (statement of Dr. John P. Seward, Board Member, American Medical Association).

[37] Lawrence Lader, A Private Matter: RU 486 and the Abortion Crisis. Amherst, N.Y.: Prometheus Books, 1995, 135-136.

pills.[38] In the interim, she and Lawrence Lader gained widespread publicity concerning RU-486 in the media. She had a surgical abortion.[39]

In that same month, Public Media Video released a documentary financed by the Chicago abortion advocacy group, Women's Issues Network, entitled, "Science Held Hostage: RU-486 and the Politics of Abortion," hosted by Cybil Shepard. They held a screening on Capitol Hill.

In the six years since approval, mounting evidence points unavoidably to one conclusion: the political motivations for bringing RU-486 to the U.S. market overwhelmed considerations of women's health and safety.

In a September 28, 2000 interview following the announcement of the FDA's approval of RU-486, then-FDA Commissioner Dr. Jane E. Henney stated: "Politics had no role in this decision."[40] That assurance has been called into question by documents made public this year which reveal the Clinton Administration's vigorous role from 1993 forward[41] in facilitating the abortion drug's entry and approval. The actors behind these documents approached approval as a matter of logistics rather than as involving an open-minded scientific inquiry. One memorandum goes so far as to advise the Administration on how to contextualize the anticipated FDA approval of the drug in terms of "promoting women's health and maintaining the close relationship of the Administration to these [pro-choice women's] groups."[42]

However, had the FDA undertaken a thorough review of the scientific literature evaluating RU-486/prostaglandin abortions before approving RU-486, the agency would have been alerted to paramount safety concerns. Certainly, the FDA Medical Officer's Review, discussed in detail below, falls short of endorsing the safety of RU-486. Even so, only two additional studies are referenced in the Medical Officer's Review[43] apart from discussion of the U.S. clinical trials and the two so-called "pivotal French trials" conducted by the manufacturer. In light of this omission, and more significantly, in light of the FDA's approval of RU-486, one wonders why numerous studies demonstrating the inherent risks to women who undergo RU-486 abortions did not appear to influence the FDA's decision to approve RU-486.

And, in fact, such a thorough review of medical and scientific literature on RU-486 had already been published in 1991 by three women who describe themselves as pro-choice

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[38] *Benten v. Kessler*, 505 U.S. 1084 (1992).

[39] *Ibid.*, at 139.

[40] Gina Kolata, "U.S. Approves Abortion Pill; Drug Offers More Privacy, and Could Reshape Debate," *The New York Times*, September 29, 2000.

[41] See, various documents compiled by Judicial Watch, Inc.. and appended to "A Judicial Watch Special Report: The Clinton RU-486 Files," April 26, 2006, available at http://JudicialWatch.org/archive/2006/jw-ru486-report.pdf.

[42] HHS Chief of Staff Kevin Thurm, Memorandum to White House Director of Public Policy Carol Rasco, Subject: RU-486, dated May 11, 1994.

[43] Beverly Winikoff *et al.*, "The Acceptability of Medical Abortion In China, Cuba and India," *Int Fam Plan Perspect.* (1997) 23:73-78 & 89; and J.T. Jensen *et al.*, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States," *Contraception* (1999): 153-159.

feminists. A brief synopsis of some of the studies they review will help set the context for the discussion of the FDA's approval process, which follows in Part II (below).

Renate Klein,[44] Janice G. Raymond[45] and Dr. Lynette J. Dumble[46] co-authored a "comprehensive literature review and analysis of hundreds of medical and scientific articles on RU 486/PG [prostaglandin], a large percentage of which have a connection with Roussel Uclaf,"[47] the pharmaceutical company that developed RU-486 in the 1980s.

The first clinical trial of RU-486 in humans took place in October 1981 in Geneva, Switzerland after only 17 months of animal research with rats, rabbits and monkeys,[48] although the results of animal trials were not such a resounding success that they justified the rush to human trials. "RU 486 caused the death in two out of three monkeys in toxicity tests,"[49] for example. None of the eleven women in Geneva who were given 200 mg of RU-486 per day for three consecutive days died, but only nine pregnancies were terminated (eight after five days and the ninth at nine days). Furthermore, one woman claimed initially as a "success" later required uterine evacuation, and another woman needed emergency surgery and a blood transfusion due to heavy bleeding.[50] Klein *et al.* describe how the Parisian newspaper *Liberation* reported on the Geneva trial: "Liberation commented that, given these associated complications and risks, RU 486 was no 'abortion miracle.' *Liberation* also reported that RU 486 is not only an anti-progesterone but an anti-glucocorticosteroid which can take the place of cortisone in the adrenal glands, and that contraindications emanating from this double action of the drug could be a problem,"[51] as it turned out to be for two out of three monkeys.

Roussel Uclaf staff proceeded next to clinical trials on small groups of women in France, Sweden, Australia, Holland, the United States of America, England, Finland and China. The manufacturer supplied RU-486 for these trials, and its staff and consultants co-authored articles reporting on the results.[52] The success rates (defined as "a complete termination of pregnancy

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[44] Ms. Klein is a biologist, professor of sociology and women's studies and author/editor of numerous books on reproductive technologies.

[45] Then Professor, University of Massachusetts and associate director of MIT's Institute on Women and Technology.

[46] Then visiting professor of surgery at the University of Texas and senior research fellow in the University of Melbourne's Department of Surgery, Royal Melbourne Hospital.

[47] Renate Klein *et al.*, RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 4.,.

[48] *Ibid.*, at 9-10.

[49] Lawrence Lader. RU486: The Pill that Could End the Abortion Wars and Why American Women Don't Have It. Reading, Mass.: Addison-Wesley Publ. Co., 1991, 17-26, at 48.

[50] Renate Klein *et al.*, RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 10, citing Etienne-Emile Baulieu, "RU-486 as an Antiprogesterone Steroid: From Receptor to Contragestion and Beyond," *Journal of the American Medical Assn.* 262:13; 1808-1814 (October 6, 1989)..

[51] *Ibid.*, at 10.

[52] *Ibid.*

without the need for further medical intervention") using RU-486 alone ranged from 54%[53] and 61%[54] to a high of 85%[55] and 90%[56] -- at best substantially below the 99% success rate for surgical abortion.

The Kovacs *et al.* trial, finding a 61% average efficacy, illustrates some of the risks encountered in RU-486 use. A total of 37 women "with amenorrhea of 42 days or less" were given RU-486 twice daily for four days at several different levels of dosage. All patients attended three follow-up visits at one, two and five-to-six weeks after the "therapy" began. In three patients (8%) pregnancy was unaffected by the drug. Two patients required blood transfusion and curettage due to heavy bleeding, and another was found at the second follow-up visit to have an extra-uterine pregnancy. Kovacs *et al.* concluded that "treatment with RU 486 may provide a novel therapy for 'menstrual regulation' but the efficacy of the treatment needs to be improved to compete with alternatives such as vacuum aspiration."[57]

In 1984, researchers in Sweden began using a prostaglandin in conjunction with RU-486 to improve efficacy rates (achieving complete abortions in 32 of 34 women subjects, or 94%), without, however, having first undertaken basic research into the potential adverse effects arising from interactions between these drugs.[58]

In late 1988, the French Minister of Health issued approval for the marketing of RU-486 in France.[59] A distinguished committee of scientific and medical experts, which included the president of France's National Academy of Medicine, the head of Nephrology Department, Necker Hospital (Paris), research directors at the (French) National Institute for Health and Medical Research and National Center for Scientific Research, began reviewing data on 30,000 women who by then had used RU-486. In April 1990, this committee issued its scathing "Report of the International Inquiry Commission on RU 486", which faults the approval of RU-486 on several grounds and which warns of the inherent and well-documented risks of RU-

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[53] Herrmann, W.L., Wyss, Rolf, Riondel, A., Philibert, Daniel, Teutsch, Georges, Sakiz, Eduoard and Baulieu, Etienne-Emile. (1982). Effet d'un stéroide antiprogesterone chez la femme: interruption du cycle menstruel et de la grossesse au début. *C R Acad Sci Paris* 294.933-938.[The effect of an anti-progesterone steroid on women: interruption of the menstrual cycle and early pregnancy. Reports of Proceedings of the Academy of Sciences, Paris].

[54] Kovacs, L., Sas, M., Resch, B.A, Ugocsai, G. Swahn, Marja-Lisa, Bygdeman, Marc and Rowe, PJ. (1984). Termination of early pregnancy by RU 486 - an antiprogestational compound. *Contracep* 29.399-410.

[55] Couzinet, Béatrice, Le Strat, Nelly, Ulmann, André, Baulieu, Etienne-Emile and Schaison, Gilbert. (1986). Termination of early pregnancy by the progesterone antagonist RU 486 (Mifepristone). *New England Journal of Medicine* 315.1565-1570.

[56] Grimes, David A., Mishell, Daniel R., Shoupe, Donna and Lacarra, Maria. (1988). Early abortion with a single dose of the antiprogestin RU-486. *American Journal of Obstetrics and Gynecology* 158: 1307-1312.

[57] Kovacs, L., Sas, M., Resch, B.A, Ugocsai, G. Swahn, Marja-Lisa, Bygdeman, Marc and Rowe, PJ. (1984). Termination of early pregnancy by RU 486 - an antiprogestational compound. *Contracep* 29.399-410.

[58] Bygdeman, Marc and Swahn, Marja-Liisa. (1985). Progesterone receptor blockage: Effect on uterine contractility and early pregnancy. *Contraception* 32; 45-51, cited in Klein *et al.*, RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 11.

[59] Report of the International Inquiry Commission on RU 486, April 1990, available at http://www.trdd.org/RU486/RUCIEE.HTM (last visited Oct. 18, 2006).

486/prostaglandin abortions. They note cardiovascular and respiratory risks – a full year before the first such fatality, but already evident from the report of one woman who lapsed into a 36-hour-long coma during an RU-486 abortion.[60]

Among the many serious issues raised by the International Inquiry Commission on RU 486 are these:

- the "very strong anti-glucocorticoid" effect of RU-486 (with which the FDA is now familiar, following the deaths from septic shock of four California women)
- the continued uncertainty surrounding RU-486's mode of action
- the necessity of using a prostaglandin to achieve marginally acceptable effectiveness, in light of the known serious side effects of prostaglandin
- metrorrhagia in over 90% of cases, lasting from 1 to 35 days (in "many cases an emergency 'Revision Uterine' [uterine evacuation] was necessary to contain the hemorrhaging. In certain cases, the only recourse was an emergency blood transfusion, with all the risks this involves.")
- "Beyond far heavier risks [compared to] the surgical method … there is – with the medicinal method – an uncertainty about the result during 5 to 12 days," as well as
  - "failure for 5% of the women who will therefore undergo surgery,
  - "around 5 to 10% persistent hemorrhages will need medicinal or surgical treatment,
  - "absolute necessity, some days after abortion, to [perform] an ultrasound examination and a HCG dosage, to be completely sure there [are] no traces of the fetus."
- the risks to women who do not return for follow-up treatment
- recently published studies demonstrating "a strong stimulating effect by RU 486 on the growth of a breast cancerous cellular line"[61] and immune system inhibition.[62]

On immune system inhibition, one wonders how the FDA could have failed to take note of the World Health Organization's 1991 study,[63] in which "9 of the 341 women (2.6%) with complete abortion and … 5 of the 17 subjects (29.4%) with incomplete abortion" had to be given "antibiotic therapy to prevent or cure suspected genitourinary infection" during the six-week follow-up period.[64] Nearly *thirty percent* of incomplete abortions involved infection.

A last example of facts the FDA should have taken into account in the agency's review of RU-486 is the personal story of Tamara Keta Hodgson, a nurse who took part in the RU-486

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[60] *Ibid.*

[61] The referenced report cites RT Bowden, JR Hissom, MR Moore. (1989) "Growth stimulation of T47D human breast cancer cells by the anti-progestin RU-486," *Endocrinology* 124; 2642-2644.

[62] BJ Van Voorhis, DJ Anderson, and JA Hill (1989), "The effects of RU 486 on immune function and steroid-induced immunosuppression in vitro," *J Clin Endocrinol Metab* 69:1195-1199.

[63] World Health Organization. (1991) "Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. *Fertil Steril* 56: 32-40.

[64] *Id.*, at 37.

trials conducted by Dr. David Grimes in Los Angeles. In a letter published in the *Los Angeles Times* under the heading "Pros and Cons of 'Dr. Grimes' bitter pill,' " Ms. Hodgson writes:

> I took RU-486 in December, 1986, when I was three weeks pregnant. Twenty-four hours later I began to have severe cramping and started vomiting. When this had gone on for 10 to 12 hours, a friend took me to the County-USC Emergency Room. After an excruciating pelvic exam, I was given a shot of Demerol, which did nothing, and a prescription for a prostaglandin inhibitor to slow down the process, which did relieve the pain. I had mild bleeding for a few days and then six days after taking the drug, I began to hemorrhage. I continued to bleed or spot until mid-March, 1987.
>
> I'm not sure why I had such an extreme response. I chose to take the drug rather than have a surgical abortion because it had been presented to me as a relatively benign experience. I also thought it might help advance the causes of both science and women.
>
> Do I think RU-486 should be licensed in the United States? I'm not sure. I had access to many resources not available to the general population of women who might take this drug. I am a registered nurse who works at one of the most sophisticated hospitals in the world. I was cared for by the research team investigating the drug. I had no children who needed to be cared for.
>
> The same cannot be said for women of the Third World. It also cannot be said for women in the United States who do not have access to adequate health care.[65]

Despite all this, what many abortion advocates promoted as a "miracle pill"[66] has turned out to be anything but. Even before its approval, the medical community knew what American women would soon learn by experience:

- mifepristone interferes with the body's immune response[67]

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[65] *Los Angeles Times*, May 6, 1990, at E-20.

[66] David Van Biema, "But Will It End the Abortion Debate?" *Time*, June 14, 1993; available at http://www.time.com/time/magazine/article/0,9171,978680,00.html (last visited October 20, 2006).

[67] *See*, Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in...mifepristone...enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486."). *See also*, Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors...results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of

- it is more inconvenient than surgical abortion[68]
- it is more painful[69]
- it is less effective[70]
- it is associated with more adverse events[71]
- it causes more frequent and more severe hemorrhage than its surgical counterpart[72]

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the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

See also, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[68] *See* FDA Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006):

> This method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
>
> Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.
>
> In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)...
>
> [In a comparison of medical termination of pregnancy with surgical termination,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion...[and] increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients... On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients...

[69] *See, e.g.,* B. Elul, et.al, *Side Effects of Mifepristone-Misoprostol Abortion Versus Surgical Abortion, Data From a Trial in China, Cuba, and India*, Contraception 59:107-114, 111 (1999): China—60.3% chemical, 36.0% surgical patients experienced pain / cramps; Cuba—89.2 % chemical, 65.4% surgical; India—61.9% chemical, 36.8% surgical.

[70] *See, e.g.,* Beverly Winikoff, et. al., *Safety, efficacy and acceptability of medical abortion in China, Cuba, and India: A comparative trial of Mifepristone-misoprostol versus surgical abortion*, Am. J. Obstet. Gynecol. 431, 434 (Feb. 1997). Failure Rates: China—chemical 8.6%, surgical .4%; Cuba—chemical 16.0%, surgical 4.0%; India—chemical 5.2%, surgical 0%.

[71] *See, e.g.,* E. Cabezas, *Medical versus surgical abortion,* 63 Internat. J Gynecol. & Obstet. Supp. 1, S141, S144 (1999). Cramping: chemical 60.0%, surgical 48.3%; Nausea: chemical 30.6%, surgical 8.9%; Vomiting: chemical 15.1%, surgical 2.0%.

[72] *See Ibid.,* chemical abortion patients experienced 2.3 days of heavy bleeding, 4.8 days of normal bleeding, and 4.9 days of light bleeding compared to 0.3, 1.8, and 3.3 days for surgical, respectively. Furthermore, 50.8% of chemical abortion patients bled more than expected, compared to 7.3% for surgical patients; and 64.1% of chemical abortion patients bled longer than expected, compared to 18.7% of surgical abortion patients. *See also,* Y.F. Chan, et.al.,

The safety issues associated with RU-486 are discussed in depth in Section III, below.

III. RU-486 APPROVAL IRREGULARITIES

Since FDA approved RU-486 in September 2000, a number of criticisms have been lodged against FDA alleging procedural irregularities in the approval process.[73] The Subcommittee investigators were aware of these criticisms and requested information from FDA regarding the issues raised by opponents of the approval. This section assesses the claims made and FDA's responses to the following allegations: 1) that FDA's approval was based solely on data from uncontrolled trials; 2) that FDA used Subpart H unlawfully when it approved the drug and, furthermore, that the clinical data used in support of the application was insufficient to satisfy Subpart H requirements; and, 3) that FDA unlawfully mandated the unapproved use of a drug, misoprostol, as part of the RU-486 abortion regimen.

A. The Approval was Unlawfully Based Solely on Data from Uncontrolled Trials

FDA's reputation as the world's foremost regulator of drug products is based largely on the rigor which it demands for data submitted in support of drug applications. The law requires, in Section 505(d)(5) of the Food, Drug and Cosmetic Act, that FDA shall not approve a drug when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[74] "Substantial evidence" means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ."[75]

Over the years, FDA's high standard in supervising the production of clinical trial data has been referred to as its "gold standard." Typically, FDA requires data from two clinical trials that are randomized, blinded and controlled against a "comparator" – often a placebo but more typically an alternative therapy.[76] FDA's Section 314.126(e) indicates that "[u]ncontrolled

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Blood Loss in Termination of Early Pregnancy by Vacuum Aspiration and by Combination of Mifepristone and Gemeprost, Contraception 47:85-95, 90 (1993): Groups receiving 200mg, 400mg, and 600mg of mifepristone experienced an average loss of 84.1ml, 99.9ml, and 101.4ml of blood respectively (ranges were 16.8 - 371.3ml, 16.7 - 524.3ml, and 20.8 - 472.4ml, respectively) compared to an average blood loss of 53.2ml for patients undergoing a vacuum aspiration abortion (range of 29.3ml - 226.0ml).

[73] For example several groups have filed a "citizen petition" with FDA regarding RU-486's approval. *See* Citizen Petition of the American Association of Pro Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America, Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation, Docket No. 02P-0377 (filed Aug. 20, 2002) ("Mifeprex Citizen Petition"). On October 10, 2003, these groups filed a response to the Danco Laboratories and the Population Council's Opposition to the Citizen Petition which was filed in March 2003. These documents are available in FDA Docket No. 02P-0377.

[74] 21 U.S.C. § 355(d)(5).

[75] 21 U.S.C. § 355(d).

[76] FDA issued a guidance document in 1998 ("Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," May 1998)("FDA Clinical Evidence Guidance") that outlines the

studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness."[77] The question of whether the RU-486 trial data was produced solely by uncontrolled clinical trials was examined by the Subcommittee investigators.

The French and American trial data were generated by trials in which the participants were given mifepristone and misoprostol to chemically end pregnancies. The RU-486 regimen was judged to have been effective, "defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[78] The studies measured the rate at which RU-486/misoprostol abortions succeeded or failed at different gestational ages.

However, neither the French nor American RU-486 trials randomized trial participants concurrently against either a placebo or the most similar RU-486 alternative, first-trimester surgical abortion.[79] Neither the French trials,[80] nor the American trial was concurrently controlled.[81] Furthermore, no discussion of controls can be found in FDA analyses of the French trials[82] or in the Spitz Study[83] that reported the results of the U.S. trial. Thus, the question arose as to whether the RU-486 trials were in fact uncontrolled.

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requirements of its drug trial policies with respect to proving effectiveness. Additionally, FDA has signed on to the principles enunciated in documents produced by the International Conference on Harmonization on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH").

[77] 21 C.F.R. § 314.126(e).

[78] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

[79] Blinding would have been very difficult to achieve with respect to the medical personnel performing the surgical abortion or dispensing the drugs to the patient, but blinding of abortion evaluators might have been achievable. In any event, scientifically rigorous randomized and concurrently controlled trials could have been performed with limited or no blinding.

[80] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone), at 2-4 (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[81] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[82] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone) (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[83] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

At the Subcommittee's May 17, 2006 hearing, *RU-486: Demonstrating a Low Standard for Women's Health?,* Dr. Woodcock, Deputy Commissioner for Operations for the Food and Drug Administration, asserted in her written testimony for the Subcommittee that "[FDA's] finding of drug effectiveness was based on a comparison to a historical control of the expected rate of continued pregnancy."[84]

In response to a post-hearing Subcommittee question, FDA noted that the historical control, used in the RU-486 clinical trials, comprised of "the well-established data and pool of medical knowledge concerning both the natural course of pregnancy itself, including the well-documented rate of spontaneous abortion or miscarriage (less than 20%), and surgical abortion."[85] We take this to mean that the spontaneous abortion rate and the rate of induced abortion were together subtracted from the expected rate of ongoing pregnancy. It is important, then, to examine the FDA's claim that the French and U.S. trials were historically controlled.

First, FDA's assertion that the French and U.S. trials were historically controlled appears to be a *post hoc* assertion. There is no mention of any control group in the Spitz Study;[86] the word "control" does not appear in the article. Moreover, an FDA statistician reviewing the French trial data asserted that "[i]n the *absence of a concurrent control group* in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy"[87] (emphasis added). The reviewer made no mention of a historical control to which mifepristone would be compared, and it is well known that controls have to be specified *before* trials are performed. The lack of a prior delineation of the controls demonstrates that FDA's claims are not supported by the record.

Second, the U.S. RU-486 trials were conducted with specific groups of persons excluded. The Spitz Study[88] lists those disqualified from participation as follows:

> "Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more

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[84] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

[85] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[86] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

[87] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone) at 7-8 (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[88] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously.[89]

Yet when FDA was asked what populations were excluded from its control group, the Subcommittee was told that "[a] historical control group does not include specific individuals, but rather is based on experience historically derived from the adequately documented natural history of the condition."[90] FDA made this additional point: "Thus, historical control populations usually cannot be assessed with respect to certain variables, such as the inclusion or exclusion of specific sub-populations."[91] This answer is methodologically insufficient, and it underscores the conclusion that, regardless of FDA's statement to the contrary, these trials were uncontrolled. The trial and control groups must be matched to each other in almost all possible ways if there is to be a meaningful control. If it was not possible to match the populations with the historical data set, then a concurrent control should have been used.

Finally, FDA allowed the use of uncontrolled trials for medical abortion because it defined the clinical endpoint too restrictively.[92] Neither spontaneous nor medical abortions produce only simple zero or one outcomes – that is, one-dimensional instances of success or failure. Not all abortions, whether spontaneous or medical, pass by themselves. Many require surgical intervention to be completed, or serious complications may ensue. FDA's cramped definition of RU-486 "effectiveness" ignores this.[93] A control should have been used in the RU-486 trial that compared different methods of producing the experimental outcome – first-trimester pregnancy termination – while assessing each method's ability to manage highly predictable, regular complications of medical abortion (*i.e.*, hemorrhage, incomplete abortion). As the International Conference on Harmonization[94] has noted, "non-defined" external controls

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[89] *Ibid*, at 1241-2.

[90] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[91] *Ibid.*

[92] *Ibid.*

[93] *Ibid.* ("In the case of medical abortion, determining the effectivness of the drug is straightforward, because it is relatively easy to determine whether the pregnancy has been terminated. Therefore, it is unnecessary to utilize a randomized clinical trial design.").

[94] FDA, "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Notice*, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The International Conference on Harmonization "is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health." *See* www.ich.org (last visited October 10, 2006).

– those in which "a comparator group [is] based on general medical knowledge of outcome" – are "particularly dangerous" and "such trials are generally considered uncontrolled."[95] Such a characterization pertains in instances like this in which the study's dependent variable (i.e., the termination of pregnancy) has been defined so narrowly as to give the false impression of complete knowledge of a simple medical outcome.

B. FDA's Abuse of Subpart H

RU-486 was approved through an important part of FDA's drug approval rules called "Subpart H."[96] In the Subcommittee's May 17 hearing, Dr. Woodcock told the Subcommittee, "FDA approved the Mifeprex NDA [new drug application] under Subpart H at the sponsor's request because the Agency determined that post-marketing distribution restrictions on the product were necessary to ensure its safe use."[97]

These rules were promulgated by FDA in 1992 as part of an attempt to correct perceived deficiencies in FDA's approval process made apparent by the need to quickly develop drugs for HIV/AIDS patients. However, in order to benefit from the provisions contained in Subpart H (*e.g.*, its restricted distribution provisions in the case of RU-486) certain conditions must be satisfied, and in the RU-486 instance, Subpart H was unlawfully used for its approval.

Inducing Medical Abortion Does Not Qualify for Subpart H

Supbart H can only be applied to drug products "that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses*…."[98] (emphasis added). FDA was aware of this requirement, and FDA asserted in its approval memo to the Population Council "that the termination of an unwanted pregnancy is a *serious condition* within the scope of Subpart H…."[99] (emphasis added).

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[95] *FDA Guidance (ICH E10): Choice of Control Group* at 5 (§ 1.3.5). Section 2.5.4 adds the following point to this discussion: "An externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course. It is often possible, even in these cases, to use alternative, randomized, concurrently controlled designs."

[96] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).. The Subpart H rules are found at 21 C.F.R. § 314.500ff.

[97] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf. We note that the Mifeprex Citizen Petition references a letter from Sandra Arnold of the Population Council to FDA, dated Sept. 6, 2000, in which she vociferously protests Mifeprex's approval under Subpart H. Mifeprex Citizen Petition at 20 (". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider.").

[98] 21 C.F.R. § 314.500.

[99] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4

Linguistic gymnastics notwithstanding, pregnancy or the termination of pregnancy is not a "serious or life-threatening illness," and therefore does not fall within the defined reach of Subpart H; the term "serious condition" is not found in the Subpart H rule. Subpart H is intended for the treatment of "serious or life-threatening illnesses," not conditions. There are situations in which pregnancies become serious or life-threatening, but the underlying condition is not "serious or life-threatening." Moreover, pregnancy itself is not an illness. There are situations in which serious or life-threatening complications may arise, but these are atypical events.

It is difficult to find a credible counter-argument from FDA or any private party defending the use of Subpart H to approve RU-486. This is not a mere technicality. If the condition being treated did not qualify for Subpart H approval, then the various restrictions that could be imposed pursuant to Subpart H to ensure the safe distribution of the drug would not have been available to the agency.

The FDA imposed several such restrictions on the distribution of Mifeprex.[100] (These restrictions, however, are less rigorous than what was initially proposed prior to approval.[101])

Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
- Has read and understood the prescribing information of Mifeprex
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going

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Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[100] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[101] FDA "Division Director Memo to File" on Mifepristone NDA, September 17, 1996 (on file with the Subcommittee): "The applicant has appropriately proposed that drug distribution be limited to licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and in the performanceof surgical abortion) who will attend educational seminars on the safe use of this regimen." The final restrictions allow for distribution under the supervision of a physician, rather than limiting it to licensed physicians, and do not require educational training on the safe use of the regimen.

pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure

- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
- Must record the Mifeprex package serial number in each patient's record

With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:

- Secure manufacturing, receiving, and holding areas for the drug
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
- Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
- Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

In addition, the Population Council agreed to two post-marketing studies on the effects of RU-486 on women[102] (though earlier reviews considered six post-marketing studies, four of them were dropped when the drug was approved[103]). In the six years since the approval of RU-486, these studies have not been completed.[104]

The RU-486 Trials Did Not Establish a "Substantial Benefit" for Subpart H

In addition to being intended for drug products studied for their safety and effectiveness in treating serious or life-threatening illnesses, Subpart H is intended only for those products that "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[105] FDA's Approval Memo stated that, for RU-486, "....[t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[106] The French and American clinical trial data did not satisfy the requirements established in the

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[102] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[103] Center for Drug Evaluation and Research, Food and Drug Administration, Office Memo to Population Council (documenting the approval action for RU-486) September 28, 2000. Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[104] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (July 31, 2006) (on file with Subcommittee).

[105] 21 C.F.R. § 314.500.

[106] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

Subpart H rules for establishing a meaningful therapeutic benefit to patients over existing treatments.

First, RU-486 was not approved for a medical indication intended for only the treatment of patients who were intolerant of surgical abortion. It was approved to treat the general population of women seeking first-trimester abortions. FDA baldly asserted that there was a clinical benefit for chemical abortion, and made no effort to produce statistical evidence of an actual benefit.

Second, surgery is an integral part of the RU-486 abortion process, because a substantial proportion of women require D&C's after beginning the mifepristone regimen. Therefore, women who have RU-486 abortions must be able to tolerate the surgical procedure. This fact alone makes it all the more difficult to accept FDA's bald assertion of a meaningful therapeutic benefit above that presented by surgical abortion. While such a benefit may exist, the law requires FDA to make its judgments based on scientific evidence. Subpart H requires that both safety and effectiveness be established for the Subpart H drug above the existing standard of care. At the very least, FDA should have required the drug sponsor to conduct non-inferiority trials to generate data for the drug application.

Third, even though some women may prefer RU-486 abortions over surgical abortions, that fact does not establish the existence of a therapeutic benefit in and of itself. One can imagine numerous ways of delivering therapies that are more desirable for the patient – for example, pills rather than injection – but FDA must establish this fact statistically.

Fourth, it appears that no concurrently-controlled trials comparing medical and surgical abortion were required by FDA, because the Agency already knew that medical abortion—i.e., abortion by RU-486—is unambiguously inferior to surgical abortion with respect to safety and effectiveness. Prior to the approval of the RU-486 NDA, the FDA medical officer made the following observations about studies that had compared medical and surgical abortion:

> [In a study comparing medical and surgical abortion in India, Cuba, and China (n = 1373)], [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India).... Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients....[107]
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> [In another non-concurrent study of 377 patients comparing mifepristone to surgical abortion in the U.S patients], [f]our mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine mifepristone

[107] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4).... Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients... Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients.... Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients."[108]

Given these comments, it is impossible to conclude that RU-486 medical abortions provide a meaningful therapeutic benefit over surgical abortion. Consequently, FDA's approval of the RU-486 NDA using Subpart H was unjustified and unlawful.

C. The Highly Unusual Placement of Misoprostol on the Mifeprex Label

When FDA approved the Population Council's RU-486 application it also mandated the use of another drug, misoprostol, as part of a two-drug abortion regimen. The use of misoprostol was not only an unapproved or off-label use – it was actually contraindicated at that time.[109] This aspect of the approval highlights another irregular component of FDA's approach to reviewing the RU-486 NDA. Shortly after FDA's approval of mifepristone, Peter Barton Hutt, a former FDA general counsel and noted commenter on food and drug law, told the Wall Street Journal that FDA appeared to have created "an extraordinary precedent", because FDA was "seemingly encouraging a drug's unapproved use."[110] He added that the agency is in an "embarrassing and uncomfortable position."[111]

The Subcommittee's questions to FDA on this matter have produced some information but no clear sense as to what FDA's policy is with respect to placing off-label or contraindicated drug uses on another drug's label.[112]

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[108] *Ibid.*

[109] On April 17, 2002, the misoprostol label was amended to remove "the contraindication and precaution that Cytotec should not be used in women who are pregnant."

[110] Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

[111] *Ibid.*

[112] In addition to questioning the FDA on this matter, the Subcommittee has looked for, and failed, to find any FDA Guidance documents on this topic.

Attention is drawn to two problems. First, it is well known that the NDA-holder for misoprostol (Searle) did not want to have its product used or labeled to reflect off-label uses as an abortifacient.[113] Thus, FDA mandated misoprostol's use in this abortion regimen and placed information about Searle's product on the Mifeprex label. Second, the entire edifice of FDA's regulation of drugs rests on the principle that only indications whose effectiveness has been demonstrated with "substantial evidence" may be placed on the label. FDA has procedures by which new indications can be approved using the supplementary new drug applications. No supplementary drug application was ever filed for misoprostol's use as an abortifacient.

In her prepared testimony before the Subcommittee, Dr. Woodcock noted that the FDA was "aware that questions ha[d] been raised about the use of misoprostol, a drug indicated for the prevention of NSAID-induced gastric ulcers, in the medical abortion regimen with mifepristone, without a separate approval and labeling of misoprostol for this use."[114] She then observed that numerous cases existed "where the labeling of one drug recommends its use with a second drug without the approval of the sponsor of the second drug."[115]

This statement is troubling and warrants further investigation. First, Woodcock's use of "recommends" is grossly inaccurate. In the Mifeprex regimen, the use of misoprostol is mandated. A physician might use an off-label variant of the regimen and, therefore, use another prostaglandin, but the Mifeprex label gives very specific directives to use misoprostol.[116] The non-optional nature of the regimen is carried forward into the language of the Patient Agreement Form which states: "I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3)."[117] Second, Subcommittee investigators finds it problematic that FDA can dictate that a drug – under the proprietary control of a firm whose NDA has been approved – can be approved for a use to which it objects.

In a letter to Chairman Souder, FDA provided two examples in which non-approved uses appear on FDA-approved labels.[118] The examples relate to coronary heart disease and metastatic

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[113] See letter from Searle warning against the use of misoprostol in abortion: http://www.fda.gov/medwatch/safety/2000/cytote.htm (last visited October 20, 2006).

[114] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

[115] *Ibid.*

[116] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[117] Mifeprex Patient Agreement, Item # 6, available at http://www.fda.gov/cder/drug/infopage/mifepristone/patientAgreement20050719.pdf (last visited October 20, 2006).

[118] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee). *See also*, See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

breast cancer, and the relevant labels should be read to understand the comments that follow.[119] Some comments are in order. First, there is no *mandated* use of the second/off-label drug in either example. Second, in the coronary disease case, the drugs were designed and approved to work on aspects of cardiovascular system-blood pressure regulation. There is nothing unusual in this use of drugs intended to manage cardiac failure.

These facts provide a qualitative difference with the Mifeprex regimen in which misoprostol was *not* designed to work to produce abortions – or uterine contractions for that matter. Rather, misoprostol was a medication intended to protect the gastro-intestinal tract from adverse events related to the use of non-steroidal anti-inflammatory medication – an indication far removed from misoprostol's novel application as an abortifacient.

Finally, FDA's Herceptin/Taxol example is somewhat disingenuous. After reading each drug's label, one recognizes that Taxol is approved for metastatic breast cancer treatment as a single agent, and so is Herceptin, but neither is specifically indicated for metastatic breast cancer treatment where no prior chemotherapy has been given. The combination use is approved (but not MANDATED) for patients with metastatic breast cancer overexpressing HER2 protein who have not received any prior chemotherapy.

Both drugs are approved for use in metastatic breast cancer. Herceptin's indication is more specifically tied to use when there is overexpression of HER2 protein. If there has been no other chemotherapy given then both may be used together. FDA seems to be splitting hairs when it claims that the use of Taxol in such cases is off-label. That characterization depends upon a fine distinction having to do with a specific tumor marker and whether or not other chemotherapy had been used.

The tenuousness of FDA's examples leads the Subcommittee to conclude that FDA is having difficulty finding examples that parallel the mandated, dissimilar off-label use of misoprostol in the Mifeprex regimen.

IV. SAFETY

Since the introduction of RU-486 to the U.S. market, the FDA has acknowledged, as of May 2, 2006, the deaths of six women associated with the drug, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection.[120] These and other cases have added up to a total of 1070 adverse event reports (AERs) as of April 2006.[121]

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[119] The relevant information can be found using the website: <www.rxlist.com>.

[120] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[121] Numbers do not convey the full story. More telling are the first-hand accounts of women who have lived these events. Below are some examples from the Individual Safety Reports (ISRs) which describe in detail the type of experience RU-486 chemical abortion has turned out to be (mistakes are as they appear in the originals):

Event of January 1, 2000, reported September 27, 2000, one day before the approval of Mifeprex: "I was issued RU-486 in effort of obtaining an abortion. I followed directions exactly, and after taking the ru-486, I was in

excrutiating physical pain, for at least 12 hours straight and I was bleeding extremely excessively. I was bleeding through my pants but was in so much pain I couldn't even clean myself. It was the worst physical pain I've ever experienced in my life. This extreme pain was constant the whole 12 hours, it did not let up at all the whole time. I vomited continuously but couldn't even hold my head up. I had unbelievable abdominal pains, I can't even put in words. I couldn't speak, eat, drink, sit up, and had difficulty breathing. The only thing I could do was lie on the floor and pull my hair to deal with the pain. I couldn't clean myself or go to the bathroom, I thought I was going to die. After about 7 hours of this, I really wanted to die because I couldn't take the pain anymore. I wanted to call the hospital but I was hours from any hospital because I went to our cabin in a remote area to have privacy during this time. The administering clinic was closed since it was the weekend.... I was not informed of the extent of these side effects, I was told it would be just like a menstrual period. I never would have taken this had I been properly informed, even of the possibility of those effects...I was not told that this drug was experimental and not approved by the FDA...I believe they outright lied to me...when I returned to the clinic after the abortion was complete, they were not very attentive or interested in me, I explained to them my pains even though they didn't ask me any questions. I filled out a questionairre that they gave me before I took the drug and they said I have to do the questionnaire ever couple hours during the abortion, but when I offered it to them upon return, they didn't even want the questionaire, they didn't take it."

Event of July 26, 2002, reported September 28, 2002: "28 year old Gr5. Para 2 Ab 2 at 6 weeks 5 days gestation received 200 mg Mifeprex on [redacted] and inserted 800 mcg misoprostol vaginally on [redacted] at 11:00 a.m. The bleeding was 'normal' until 3:30 p.m. when it became heavier. That evening she stated 'it was like water coming out of me' and she felt dizzy. That evening she reported that she briefly 'passed out' twice. She went to an emergency room and received [missing] litres of IV fluid and had a D&C. Her hemoglobin on arrival was 8.7 gm/dl and was [missing] gm/dl after the D&C. She was started on iron supplementation. On [redacted] her hematocrit was 28% at the clinic and she reported that she was resting, on limited to light activity and doing well."

Event of August 15, 2004, reported July 25, 2005: "I took RU-486 last year and it caused me serious problems. After 15 days after taking it I hemorrhaged while at work requiring subsequent D&C, then had an infection that would not go away despite multiple antibiotics. I ended up being hospitalized and having multiple tests due to the infection and pain. I was hospitalized for four days in september of last year. Even after being hospitalized I was very ill for quite some time. I believe it took me until December to fully recover, during this time I lost quiet a bit of weight and had to enter counseling as a result of all the problems after using RU486."

Event of October 31, 2002, reported August 13, 2005: "Previous to 2002 I had two pregnancies and two live births...In 2002, 2003, and 2004, I had a three abortions at a very early stage, using the 'French' pill—RU-486—with each being almost exactly a year apart. I had the same experience each time. I developed a very bad case of bacterial vaginosis...I also was told to insert the final pill vaginally in all three cases. I had no idea it could even be taken orally."

Event of September 8, 2004, reported August 17, 2005: "I was given 2-step Abortion Pill. In the middle of the night I was awoken by severe abdominal pains. Having had endometriosis has built my pain tolerance quite high, but this pain was excruciating. Between the pain and diarrhea, I wanted to pass-out. I laid on the cold tile of the bathroom floor for 4 hours to keep me from fainting and because I couldn't get up. I thought it would eventually taper off, but after 4 hours I was exhausted and couldn't tolerate the pain. I yelled until my sister woke up to help me and asked her to call 911. She knew that I never go to the hospital, much less ask for 911, she immediately called. At the hospital, blood tests –b-hcg- kept coming back positive and I was still in alot of pain. They sent me for ultrasounds, blood tests again, and pelvic exams. I asked for more morphine, but they told my sister that they gave me the maximum dose and were surprised that I was still moaning of pain. The doctor said that my body was going through labor over and over, but wasn't ridding of anything. After the 3rd pelvic exam and blood test, the HCG count started coming down."

Event of December 14, 2005, reported December 27, 2005: "Approximately 2 1/2 weeks after taking Mifeprex and Cytotec to end a pregnancy, I began having very heavy bleeding. This was after I had not bled for a week, and after a 2 week follow up at a clinic—in which was told I was fine—I began hemorraging on the evening of the 14th, passing clots approximately 3 inches in size. I went through approximately 7 pads in 2 hours. The clinic wanted me to wait until the morning to get care from their facility, but when we called the local ER, they told me I needed to come in right away to get examined. I was cold, weak, and fatigued during the 2 hours my bleeding was excessively heavy. Unfortunately I was not able to make it into the ER because I am a single mother of 4, and had noone to care

A. Adverse Events for RU-486

These reports are based on the FDA's Adverse Event Reporting System (AERS), a voluntary system, with inherent underreporting. Common estimates of the proportion of adverse events actually captured by FDA in AERS are from one to ten percent. FDA acknowledges that it does not capture all adverse events associated with a drug: "When evaluating reports from the AERS system, it is important to recognize several caveats. First, *accumulated case reports cannot be used to calculate actual incidences of adverse events or estimates of risk for a product, as the reporting of adverse events is a voluntary process with inherent underreporting*"[122] (emphasis added).

The Government Accountability Office (GAO) has also commented on the underreporting of Adverse Events: "FDA cannot establish the true frequency of adverse events in the population with AERS data. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem, and it makes comparisons of risks across similar drugs difficult."[123]

FDA nonetheless claims that it is capturing most adverse events associated with RU-486: "Because healthcare professionals who prescribe Mifeprex have agreed in writing" (with the manufacturer, Danco, *not* the FDA) "to report 'any hospitalizations, transfusions or other serious events' to the manufacturer, FDA believes that there are unlikely to be significant numbers of serious adverse events, including deaths, associated with Mifeprex that have not been reported to the Agency."[124]

During the Subcommittee staff's review of the 1070 Adverse Event Reports that had been reported through April 2006, ISRs were found that had been submitted through MedWatch, the voluntary reporting mechanism for AERS, rather than through Danco. FDA acknowledged that these reports were not matched by reports submitted through Danco,[125] undermining the Agency's claim that it is capturing most adverse events.

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for my children. Luckily for me, the bleeding lessened. I was told it was 'normal' to bleed for up to 4 weeks, but I am NOW at day 32 and still bleeding."

[122] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[123] Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process GAO-06-402 March 31, 2006.

[124] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (July 31, 2006) (on file with Subcommittee).

[125] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (June 30, 2006) (on file with Subcommittee).

In light of FDA's repeated claim that it captures most RU-486-related adverse events—despite the Agency's own acknowledgement of underreporting and experience to the contrary—it is important to note that there is no true enforcement mechanism, either by Danco or the FDA, for ensuring that doctors report all adverse events, and there is little incentive on the part of the prescribing physician to do so.[126]

Even Danco has noted that the FDA's "obligatory" reporting system is of little value. In 2003, Dr. Richard Hausknecht, Medical Director for Danco, wrote that "[t]he obligatory reporting of adverse events is limited to transfusions, hospitalizations, ongoing pregnancies or 'other serious adverse events,' which allows considerable subjective judgment on the part of the providers. In addition, the reporting of other common adverse events may not be reported at all."[127]

Moreover, emergency room personnel and medical professionals who do not prescribe RU-486, but who may likely treat the infected or hemorrhaging patient, or provide surgical intervention, *have no obligation whatsoever to report adverse events for RU-486*, even assuming that the healthcare worker is aware the patient took the RU-486 drug regimen.[128] In such scenarios, prescribing physicians may remain unaware of adverse events that take place after they administer RU-486, alleviating them of reporting requirements. This underscores the fact that there is not an accurate picture of the total adverse events that are being experienced with this drug.

In addition to the fact that there is no accurate number of adverse events to serve as a realistic "numerator" for evaluating the rate of adverse events actually being experienced in the population, the FDA does not use an accurate figure for the true number of patients who have taken RU-486 as a "denominator." Rather, FDA accepts and reports "estimates" proposed by Danco. The most recent estimate is that 612,000 women in the U.S. have used RU-486 as of July 24, 2006.[129]

This estimate is likely inflated, since Danco arrives at its estimate by basing it on the number of packages sold (in three-pill packages of 200 mg pills) and multiplying that number by three to account for the number of doses that are given at the off-label 200 mg dose (rather than

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[126] Although RU-486 is approved for use through 49 days of pregnancy, it is commonly prescribed in the United States up to 63 days of pregnancy. Physicians also commonly prescribe a dosing regimen that is different from that approved by the FDA. Therefore, it has been suggested that in fact there is a *dis*incentive on the part of prescribing physicians to report adverse events that may be attributed to a physician's negligence or willingness to prescribe a regimen that is outside the FDA-approved regimen for RU-486.

[127] Hausknecht, R., "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003) 463-465.

[128] Treating personnel might never know that a woman has taken RU-486; Women who seek medical treatment for adverse reactions after RU-486 may be too sick to disclose, may fail to disclose, or may simply refuse to disclose (because she does not want it in her medical record) that she has taken the RU-486 drug regimen.

[129] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17. 2006) (on file with Subcommittee).

the FDA approved 600 mg dose).[130] That Danco is allowed to provide a loosely-figured *estimate* flouts the restricted approval provision for RU-486, which requires Danco to distribute the drug with a tracking system allowing the company to track packages "to the patient level while maintaining patient confidentiality."[131]

For FDA to rely upon guesses as a basis for understanding safety problems with RU-486 is highly problematic. Danco's estimate is used as the denominator for determining the rate of adverse events associated with the drug. The larger the denominator, the lower the percentage of adverse events. This inaccuracy of using Danco's estimate is inexcusable in light of the way the estimate is relied upon to determine and discuss the rate of adverse events associated with RU-486.

B. RU-486 Safety Issues Known Prior to Approval

Prior to FDA's approval of RU-486, the Agency's own medical experts recognized that any benefits that could be gained from the use of this drug for a "medical abortion" were limited at best and that significant dangers were inherent in its use. These dangers are especially acute when compared to surgical abortion. According to the FDA's medical reviewer, writing before the drug's approval:

> This method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
>
> Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.
>
> In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)...
>
> [In a comparison of medical termination of pregnancy with surgical termination,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical

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[130] Richard Hausknecht, Medical Director for Danco, described how Danco estimates the usage figures for RU-486: "Denominators... were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), ...[an] estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices...[and by] [a]djusting for utilization patterns of providers." *Contraception* 67 (2003): 463-65.

[131] CDER Office Memo to Population Council, September 28, 2006. At http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited September 28, 2006).

abortion…[and] increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients… On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients….[132]

The negative physical experience of RU-486 was explained this way by Dr. Tom Tvedten, an abortion provider in Little Rock, Arkansas: "With medical termination, the discomfort is significant because they have to go through mini-labor…There's a lot of hard cramps and usually significant bleeding. It's cheaper, safer and less painful to have a surgical termination."[133]

In fact, as explained in the RU-486 label, "nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction,"[134] including: abdominal pain; uterine cramping; nausea; headache; vomiting; diarrhea; dizziness; fatigue; back pain; uterine hemorrhage; fever; viral infections; vaginitis; rigors (chills/shaking); dyspepsia; insomnia; asthenia; leg pain; anxiety; anemia; leucorrhea; sinusitis; syncope; endrometritis / salpingitis / pelvic inflammatory disease; decrease in hemoglobin greater than 2 g/dL; pelvic pain; and fainting.[135]

The FDA's Medical Officer's review notes that, "[m]ore than one adverse event was reported for most patients…Approximately 23% of the adverse events in each gestational age group were judged to be severe."[136]

In addition to these known, startling adverse effects, of which the FDA was aware during the RU-486 NDA review process, the incredibly high failure rate of the drug was also known, averaging 14.6% in the U.S. trial testing the drug through 63 days gestation.

The FDA's Medical Officer's review noted that in the U.S. trial of 2015 women, "[a] total of 295 patients were classified as having failed medical abortion."[137] This represents a

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[132] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[133] John Leland, *Under Din of Abortion Debate, an Experience Shared Quietly*, N.Y. TIMES, Sept. 18, 2005, *at* http://www.nytimes.com/glogin?URI=http://www.nytimes.com/2005/09/18/national/18abortion.html&OQ=_rQ3D1&OP=41647c1fQ2FQ2AQ7EklQ2AbBG)ABB7FQ2AFqqjQ2AqQ2FQ2A42Q2A-_7VB-_YQ2A42_lBA7VB-vC7KY. (Quoting Dr. Tom Tvedten of Little Rock, Arkansas).

[134] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[135] *Ibid.*

[136] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[137] *Ibid.*

failure in 14.6% of total patients. "Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure."[138]

The "best" outcome was in the patient group consisting of women whose pregnancies were less than or equal to 49 days. In this group, 7.9% of patients required surgical intervention after taking RU-486. As the gestational age increases, the failure rate of RU-486 increases rapidly, to 17% in the 50-56 days gestation group, and 23% in the 57-63 days gestation group.

By any objective standard, a failure rate approaching eight percent and requiring subsequent surgical intervention as the "best" outcome is a dismal result. Nonetheless, the Medical Officer stated that "[t]he 92% success rate in the ≤ 49 days group is an acceptable one."[139] This failure rate, along with the anticipated adverse events that patients would experience, is explicit in the FDA Medical Officer's review, and also part of the RU-486 label.[140]

Despite these known problems with adverse events and high failure rates, the FDA recommended and gave approval for distributing this drug to women.

B. Post-Approval Hemorrhage, Infections and Deaths

As stated above, the FDA has acknowledged the deaths of six U.S. women associated with RU-486, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions and 88 cases of infection. [141] A quarter all the patients were hospitalized.[142] These and other cases add up to a total of 1070 adverse event reports (AERs) as of April 2006.

A review[143] of only a portion of all the reported AERs demonstrates in real world experience how women have suffered after taking dangerous drug. Out of only 607 unique adverse events submitted to the FDA, the high number of serious and life-threatening events is startling:

> The most frequent [adverse event reports] were hemorrhage (n=237) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious case; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life-threatening) and

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[138] *Ibid.*

[139] *Ibid.*

[140] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[141] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[142] *Ibid.*

[143] M. M. Gary, D. J. Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, The Annals of Pharmacotherapy, February 2006, 40.

43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology, 1 was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.[144]

Since this review by Gary and Harrison, there have been hundreds more adverse event reports and two additional reported septic infection deaths. Nearly all among the afflicted and dead who experienced these serious adverse events following RU-486 were healthy women of child-bearing age. (This is in sharp contrast to other drugs with inherent risks—Viagra, for example—which result in adverse events often after repeated use over long intervals of time, in patients with other risk factors associated with age or disease.) Without access to emergency room services, women who suffered severe hemorrhage would have died.

In total, there are eight known deaths following RU-486: four Californians and one Canadian from *C. Sordellii* septic infection; a Tennessee woman with ruptured ectopic pregnancy; a Swedish teen, from massive hemorrhage; and a British female, from "unknown etiology," (but her clinical presentation of shock and an autopsy revealing one liter of blood in her stomach makes sepsis a plausible etiology).[145]

Five of the eight known deaths following the use of RU-486 have been the result of a toxic shock-like syndrome initiated by the bacteria *C. Sordellii.* This bacteria is thought to exist in low numbers in the reproductive tracts of many women and is normally contained by the immune system.[146] Experts in immunology,[147] pharmacology[148] and maternal-fetal medicine[149]

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[144] *Ibid.*

[145] *Ibid.*

[146] Letter to the Editor, James A. McGregor and Ozlem Equiles, *Risks of Mifepristone Abortion in Context*, Contraception 2005, 71: 161.

[147] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in...mifepristone...enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486.")

[148] *See,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors...results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

have suggested that because RU-486 interferes with the immune response, the bacteria, if present, are then able to flourish, causing a widespread, multi-organ infection in the woman.

The infections are *not* accompanied by a fever, and symptoms match those that are expected after taking the RU-486 regimen (cramping, pain, bleeding, nausea, vomiting), making detection of the fast-spreading infection difficult. Each of the women infected with *C. Sordellii* after RU-486 were dead within five to seven days.

The FDA describes the clinical presentation of *C. Sordellii* infection the following way:

- Rapid onset of influenza like symptoms (nausea, vomiting, and weakness)
- Hypothermia or *absence* of fever
- *Absence* of purulent discharge
- Localized pelvic tenderness may be *absent*
- Elevated hematocrit and marked leukemoid reaction
- Progressive refractory hypotension
- Marked edema with peritoneal and pleural effusions
- Rapidly fatal despite aggressive treatment[150] (emphasis added).

To investigate the nature of the *C. Sordellii* bacteria, the FDA and CDC held the "Emerging Clostridial Disease" workshop on May 11, 2006.[151] Workshop presenters – experts in the fields of pharmacology, immunology, and maternal-fetal medicine – noted that the rapid growth of the *C. Sordellii* bacteria likely forecloses effective treatment;[152] that there is no currently identifiable "window of opportunity" for treatment once a woman is infected, even with major interventions such as hysterectomy;[153] and that antibiotic prophylaxis was unlikely to provide any protection in the RU-486 / *C. Sordellii* context.[154] The fatality rate has been 100% for the women who contracted *C. Sordellii* infection after RU-486.

In an effort to dismiss any association between RU-486 and the *C. Sordellii* deaths, some have promoted the idea that *C. Sordellii* is linked to pregnancy and childbirth, not the abortion pill. However, in five years, five women have died from this infection after taking RU-486. In contrast, the FDA has noted that there were "only five additional cases not associated with

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[149] *See,* Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[150] Food and Drug Administration "Center Director Briefing" June 27, 2005 (on file with the Subcommittee).

[151] A full transcript for the meeting is available at: http://www.fda.gov/cder/meeting/clostridial/transcript.pdf (last visited October 13, 2006).

[152] Letter to the Editor, James A. McGregor and Ozlem Equiles, *Risks of Mifepristone Abortion in Context*, Contraception 2005, 71: 161.

[153] Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Transcript available at http://www.fda.gov/cder/meeting/clostridial/transcript.pdf (last visited October 13, 2006).

[154] *Ibid.*

mifepristone/misoprostol retrieved with a text search of the entire AERS database"[155] of 3.5 million records.[156]

Distinguishing the 100% fatality rate with this infection following RU-486 among women who were otherwise healthy, the FDA noted, "[t]he patients in these 5 [non-RU-486 related] cases had weakened or altered immune function due to chemotherapy and age (neonatal & elderly patients), and use of multiple antibiotics. None of these five cases involved intravaginal product administration and 3 cases had a fatal outcome. *In contrast to these 5 additional cases in [3.5 million] AERS, the 4 U.S. confirmed cases of Clostridium Sordellii infection with medical abortion involved healthy patients and all cases had fatal outcome*"[157] (emphasis added).

A more extensive database search for any reported *C. Sordellii* infections since 1925 found a total of eleven fatal cases related to post-partum/ob-gyn infection or to spontaneous abortion.[158] In contrast with this small number of cases (11 since 1925) five women in five years are known to have died from *C. Sordellii* following RU-486.

Experts studying the immune suppression properties of RU-486 have found that it has the ability to block innate immune response.[159] Lazar had published information as early as 1992

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[155] Memorandum, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 12, 2006, From [redacted], Division of Drug Risk Evaluation, Through: [redacted] Division of Drug Risk Evaluation, TO: [redacted] Division of Reproductive and Urologic Products. Subject: Supplementary investigations related to reports of fatal infections associated with mifepristone and misoprostol use for medical abortion. [handwritten note: DFS 4/17/06 Consult #3]

[156] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[157] Memorandum, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 12, 2006, From [redacted], Division of Drug Risk Evaluation, Through: [redacted] Division of Drug Risk Evaluation, TO: [redacted] Division of Reproductive and Urologic Products. Subject: Supplementary investigations related to reports of fatal infections associated with mifepristone and misoprostol use for medical abortion. [handwritten note: DFS 4/17/06 Consult #3]

[158] Dennis L. Stevens, M.D., PhD., *Clostridium sordellii: Clinical Settings, Diagnostic Clues and Pathogenic Mechanisms*, Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Available at http://www.fda.gov/cder/meeting/clostridial/stevens.pdf (last visited October 13, 2006).

[159] *See*, Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in...mifepristone...enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486."). *See also*, Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors...results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The

about the increase in fatal septic infection in mice after receiving RU-486, which caused the survival rate to drop dramatically from the control level of 71% to only 15%.[160] Nonetheless, the theory that RU-486 suppresses the immune system was only noted by the FDA as late as 2003,[161] and it wasn't until 2004 that the Agency conducted the minimal inquiry of a literature review to examine the immune suppression properties of RU-486:.

> "The Division of Anti-Infective Drug Products (DAIDP) reviewed the medical literature to examine the potential impact that either or both mifepristone and misoprostol might have on human immune function. They concluded, 'Systemic levels of mifepristone and misoprostol may both influence the host response to infection via their anti-inflammatory effects, respectively. In theory, *these effects may predispose an individual to infection or may predispose an infected individual to a worse outcome.* Such roles are apparently dependent on dose, timing, and rates of uptake and intracellular degradation in different target tissues'"[162] (emphasis added).

Beyond this, there is little more in the thousands of pages of documents provided to the Subcommittee to indicate an extensive FDA examination of the immune suppression properties of RU-486.

In the meantime, women who take RU-486 are exposing themselves to an exponentially greater risk of infection or death as compared to the alternative of surgical abortion. The risk of death from infection is at least ten times greater than surgical abortion during the first eight weeks of pregnancy.[163] In addition to *C. Sordellii* infection, women taking RU-486 have developed other infections following the abortion pill regimen. The FDA has acknowledged 88 reported cases of infection following RU-486.

The most frequent serious adverse event is hemorrhage, where women who lost enough blood as to require transfusions. These cases of massive hemorrhage comprise 12% of the RU-

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> combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

See also, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[160] G. Lazar, *et al.*, *Modification of septic shock in mice by the antiglucocorticoid RU 38486*, 36 Circulatory Shock 180 (1992).

[161] FDA Division of Anti-Infective Drug Products, Report of Medical Officer Consultation (Intravaginal Misoprostol), November 19, 2003, at 4 (on file with the Subcommittee)..

[162] FDA Mifeprex plus Misoprostol Postmarketing Safety Review, November 15, 2004, at 24 (on file with the Subcommittee).

[163] *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318. The mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. The rate could be higher, if an accurate numerator is used for the true number of patients who have taken RU-486.

486 AERS.[164] A review of the AERS through September 2005 finds that fifteen women suffered hemorrhages so serious that they lost over half of their entire blood volume and would have died without rapid access to emergency room services.[165]

According to Dr. Donna Harrison, who testified before the Subcommittee at the May 17 hearing *RU-486: Demonstrating a Low Standard for Women's Health?*, "In my experience as an ob-gyn, the volume of blood loss seen in the life-threatening cases is comparable to that observed in major surgical trauma cases like motor-vehicle accidents. This volume of blood loss is rarely seen in early surgical abortion without perforation of the uterus, and it is rarely seen in spontaneous abortion."[166]

As with other adverse events associated with RU-486, no risk factors for hemorrhage have been identified. Rather, they are unpredictable and sporadic.[167]

The proven health risks and demonstrated association with fatal septic infections necessarily prompt urgent consideration of this drug's immediate withdrawal from the market.

V. RECOMMENDATIONS

The high incidence of adverse events has prompted Danco, in cooperation with the FDA, to take steps to alert women and the medical community to the dangers of the drug:[168]

- "Dear Health Care Provider" Letter, April 19, 2002 (warning of danger of ruptured ectopic pregnancies).[169]
- "Dear Emergency Room Director" Letter, November 12, 2004 (warning of infection, heavy bleeding and ruptured ectopic pregnancy).[170]
- "Dear Health Care Professional" Letter, November 12, 2004 (warning of infection, heavy bleeding and ruptured ectopic pregnancy).[171]
- Updated label, December 22, 2004 (reflecting danger of infection, heavy bleeding and ruptured ectopic pregnancy).[172]

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[164] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[165] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Donna Harrison, M.D.) Available at http://reform.house.gov/UploadedFiles/Harrison%20Testimony%20-%20scan%20test.%20w%20attchmts.pdf.

[166] *Ibid.*

[167] *Ibid.*

[168] See Danco's website, http://www.earlyoptionpill.com/.

[169] Available at http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf (last visited October 14, 2006).

[170] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearER.pdf (last visited October 14, 2006).

[171] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearHCP.pdf (last visited October 14, 2006).

- "Dear Health Care Provider" Letter, July 19, 2005 (warning of the cases of fatal septic shock).[173]
- Updated label, July 19, 2005 (warning of danger of fatal *C. Sordellii* infections).[174]

In light of the significant health risks posed by this drug, the current restrictions, and the letters and label changes subsequent to approval are demonstrably insufficient to protect women from the dangers of RU-486. Rather, the FDA possesses the authority to suspend or withdraw approval of the drug under various provisions. The most important, and perhaps necessary and justified for removing RU-486 from the market, is the Imminent Hazard authority possessed by the Secretary of Health and Human Services.

"Imminent Hazard" is defined and the criteria to be considered are set forth in 21 CFR 2.5:

> (a) Within the meaning of the Federal Food, Drug and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.
>
> (b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.

Under this provision, the Secretary's decision is subject to judicial review, but the courts are deferential to the Secretary's conclusions.[175] Within the context of RU-486, the unpredictability and frequency of serious adverse event and death (discussed in Section III above) warrants withdrawal of this dangerous drug from the market.

The FDA also possesses the authority to unilaterally withdraw approval of a drug under 21 CFR 314.530. RU-486 falls into the withdrawal categories of this provision:

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[172] Available at http://www.fda.gov/cder/foi/label/2004/020687lbl_Revised.pdf (last visited October 14, 2006).

[173] Available at http://www.fda.gov/medwatch/safety/2005/mifeprex_deardoc_071905.pdf (last visited October 14, 2006).

[174] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearHCP.pdf (last visited October 14, 2006).

[175] See *Forsham v. Califano*, 442 F. Supp. 203 (D. D.C. 1977)(this case appears to be the only instance in which the "imminent hazard" authority of the HHS Secretary has invoked). See also *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of O. Carter Snead, Assoc. Professor, University of Notre Dame Law School). Available at http://reform.house.gov/UploadedFiles/Snead%20Testimony.pdf.

(a)(1) A post-marketing clinical study fails to verify clinical benefit

Since its approval, RU-486 has been associated with six known U.S. deaths of healthy women.[176] The safety problems associated with RU-486 are discussed above. Additionally, because women who visit the emergency room arrive with symptoms virtually identical to those associated with miscarriage,[177] deaths within the U.S. following the use of RU-486 may be higher, but unreported.

Moreover, as discussed above, the mortality rate for surgical abortion for the first eight weeks of pregnancy is 0.1 per 100,000.[178] The makers of RU-486 report that 575,000 women have used the drug (based on units shipped, not units prescribed, and based on the assumption that one tablet—rather than the FDA-approved three—is administered to the patient;[179] the actual number of women who have taken the drug may be much lower). Using the figure of 575,000 women having taken RU-486, this works out to a known death rate of approximately 1.39 per 100,000, nearly *14 times* greater than surgical abortion. As noted above, Subpart H drug approval is conditioned on "meaningful therapeutic benefit." The statistics demonstrate that medical abortion is far more dangerous than the existing treatment of surgical abortion, which is proof of a lack of clinical benefit.

(a)(3) Use after marketing demonstrates that post-marketing restrictions are inadequate to assure safe use of the drug product

Experience shows that post-marketing restrictions on RU-486 are inadequate to assure the safe use of the product, because the medical community has ignored them on a widespread basis. As noted earlier in this report, abortion providers routinely use RU-486 beyond the time periods approved by the FDA[180] and with dosing regimens that stray from the FDA's approved

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[176] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee).

[177] "Dear Emergency Room Director" Letter from Danco Laboratories to emergency room directors, (Nov. 12, 2004), *at* http://www.fda.gov/cder/drug/infopage/mifepristone/DearER.pdf.

[178] Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353:22 *at* 2318.

[179] *Ibid.*

[180] Some abortion providers (e.g., Planned Parenthood of New York City at www.ppnyc.org/services/factsheets/mifep.htm, Capital Care Women's Center at www.capitalcarewomenscenter.com/services.php, and Camelback Family Planning at www.camelbackfamilyplanning.com/abortionpill.html.), even advertise the availability of RU-486 through 63 days LMP, by which time the rate of incomplete abortion, infection, and other complications rises sharply. In U.S. clinical trials, the failure rate for RU-486 abortions jumps to 17% at 50-56 days LMP, and to 23% at 57-63 days LMP, from 8% at 49 days or less. Irving Spitz *et al.*, "Early pregnancy termination with mifepristone and misoprostol in the United States," *New England Journal of Medicine* 1998, 338:1241-47.

regimen.[181] While off-label use of drugs is common, it runs contrary to the entire purpose of the regulatory regime approved for RU-486 under Subpart H.

The FDA is aware of the medical community's refusal to heed the regulations it instated on RU-486. In its own words, the FDA "is aware that...some [physicians] may have chosen to use a modified version of the Patient Agreement form. However, these decisions are made by physicians exercising their own judgment about what is best for their patients."[182]

This is contrary to the detailed Risk Management Program, explained in the FDA memo detailing the drug's approval, which states: "the signed agreement form will be given to the patient for her reference and another kept in the medical records," and "[the prescribing physician] must provide each patient...with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well."[183] The FDA determined that these restrictions were critical to the safe use of the drug, and in spite of this, physicians have refused to heed them.

(a)(4) The applicant fails to adhere to the post-marketing restrictions agreed upon

Although the FDA stipulated that the manufacturer have systems in place to track the distribution of RU-486 "to the patient level," and that require physicians to "record the Mifeprex package serial number in each patient's record,"[184] Danco has not provided reliable patient numbers, but rather estimates.[185]

In addition to the FDA requiring patients to sign a Patient Agreement form, the Population Council agreed, as part of the approval process, to "auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms." It is unclear whether the Population Council, Danco, or any other entity associated with the production of RU-486 has adhered to this requirement.

(a)(5) The promotional materials are false or misleading

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[181] R. Hausknecht, "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003): 463-65: "Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg)."

[182] Letter from Patrick Ronan, Associate Commissioner for Legislation Department of Health and Human Services FDA to Hon. Mark E. Souder, (March 16, 2006) (on file with Govt. Reform Subcommittee on Criminal Justice, Drug Policy, and Human Resources).

[183] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000) (available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf).

[184] *Ibid.*

[185] Richard Hausknecht, Medical Director for Danco, described how Danco estimates the usage figures for RU-486: "Denominators... were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), ...[an] estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices...[and by] [a]djusting for utilization patterns of providers." *Contraception* 67 (2003): 463-65.

The FDA conditioned approval of RU-486 on tracking its use "to the patient level." In spite of this, the manufacturer estimates the usage of its drug for its promotional materials.[186] This affects the perceived safety of the drug, as the manufacturer may be overstating its actual usage in comparison with the adverse events reported.

Both the "Imminent Hazard" provision and the regulatory provision for approval withdrawal under Subpart H provide sufficient authority for the Administration to remove this dangerous drug from the market.

VI. CONCLUSION

The integrity of the FDA in the approval and monitoring of RU-486 has been substandard and necessitates the withdrawal of this dangerous and fatal product before more women suffer the known and anticipated consequences or fatalities. RU-486 is a hazardous drug for women, its unusual approval demonstrates a lower standard of care for women, and its withdrawal from the market is justified and necessary to protect the public's health.

[186] *Ibid. See also*, Letter from David W. Boyer, Assistant Commissioner for Legislation, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee); *FDA Announces Mifeprex Not Cause of One of Two Recent Abortion-Related Deaths*, KAISER NETWORK DAILY REPORTS, (April 11, 2006) *at* http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=36534. ("We stand behind the safety profile of the drug, which has been used by approximately 575,000 women in this country since FDA approval in 2000," quoting Cynthia Summers, director of marketing and public affairs at Danco Laboratories, originally in Wall Street Journal, April 11, 2006.)