Exhibit 13

2002 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to U.S. Food & Drug Admin. (FDA) (Aug. 20, 2002)

BEFORE THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Citizen Petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation	)))))

CITIZEN PETITION AND REQUEST FOR ADMINISTRATIVE STAY

The American Association of Pro Life Obstetricians and Gynecologists ("AAPLOG"), the Christian Medical Association ("CMA"), and Concerned Women for America ("CWA") (collectively, "the Petitioners") submit this Petition pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500-314.560); and Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355).[1] The Petitioners urge the Commissioner of Food and Drugs to impose an immediate stay of the approval by the Food and Drug Administration ("FDA" or "agency") of Mifeprex™ (mifepristone; also, "RU-486"),[2] thereby halting all distribution and marketing of the drug, pending final action on this Petition. In addition the Petitioners urge the Commissioner to revoke FDA's approval of Mifeprex and request a full FDA audit of the Mifeprex clinical studies.[3]

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[1] Federal Food, Drug, & Cosmetic Act of 1938 ("FD&C Act"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

[2] The New Drug Application for Mifeprex, which was filed by the Population Council, was approved on September 28, 2000. Mifeprex is distributed by Danco Laboratories, a licensee of the Population Council.

[3] The Petitioners will, at times, cite to documents contained in FDA's January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act request ("FDA FOIA Release") filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <http://www.fda.gov/cder/archives/mifepristone/default.htm> Since the initial release FDA has edited some of the 94 files. However, the stamped page numbers have not changed. Additionally, many footnotes refer to Appendix A to this Petition, which contains a selected bibliography.

I. ACTION REQUESTED

The Petitioners respectfully request that the Commissioner immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on this Petition. They urge the Commissioner to revoke market approval for Mifeprex in light of the legal violations and important safety concerns explained below. In addition, they request a full FDA audit of all records from the French and American clinical trials offered in support of the Mifeprex NDA.

II. INTEREST OF THE PETITIONERS

While it is true that the Petitioners have consistently opposed abortion and continue to do so, a careful examination of the claims made in this petition should alert people of conscience on either side of this issue that women are being harmed. Regardless of one's position on abortion, FDA's violations of its standards and rules have put women's health and lives at risk. The Petitioners are non-profit organizations that share a great concern about women's health issues. The American Association of Pro-Life Obstetricians and Gynecologists ("AAPLOG") is a recognized interest group of the American College of Obstetricians and Gynecologists ("ACOG"), currently representing over 2,000 obstetricians and gynecologists throughout the United States of America. The Christian Medical Association, founded in 1931, is a professional organization with thousands of physician members representing every medical specialty. Concerned Women for America ("CWA"), founded in 1979, is the largest public policy women's organization in the United States with members in every State and a total membership exceeding 500,000.

III. STATEMENT OF GROUNDS

A. SUMMARY OF THE PETITIONERS' ARGUMENTS

Good cause exists to grant an immediate stay of the agency's September 28, 2000 Mifeprex approval.[4] Good cause also exists for the subsequent revocation of that approval.[5] As established herein, (1) the approval of Mifeprex violated the Administrative Procedure Act's prohibition on agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;[6] (2) FDA's approval of Mifeprex violated 21 U.S.C. § 355 because the drug does not satisfy the safety and labeling requirements of that section; and (3) the agency approved Mifeprex despite the presence of substantial risks to women's health.

This Petition represents the latest attempt by members of the medical community and other concerned observers to warn FDA of the dangers posed by Mifeprex abortions to the health of women.[7] Women undergoing Mifeprex abortions risk, among other problems, uncontrolled fatal hemorrhage and serious bacterial infections. Mifeprex abortions particularly endanger women with ectopic pregnancies and those whose pregnancies have progressed beyond 49 days.[8]

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[4] When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Petition, "Mifeprex Regimen" will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

[5] *See* 21 C.F.R. § 314.530 ("Withdrawal Procedures").

[6] 5 U.S.C. § 706(2)(A).

[7] On February 28, 1995, Americans United for Life and other groups and individuals filed a Citizen Petition with FDA requesting it to "refuse to approve any NDA for RU 486 for use as a pharmaceutical abortifacient that does not contain adequate evidence that the drug has undergone nonclinical and clinical safety and effectiveness trials." The petitioners also set forth a number of factors for the agency to consider. Americans United for Life *et al.*, Citizen Petition (Feb. 28 1995)[FDA FOIA Release: MIF 006144-6248]; *see also*, Letter, Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Gary L. Yingling, McKenna & Cuneo (March 20, 1995) (one-page letter suggesting that the petition was prematurely filed and claiming to be a "full response")[FDA FOIA Release: MIF 006250].

[8] The gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy. On Day 49, a woman is deemed to be seven weeks pregnant, which means she has experienced 49 days of amenorrhea (time elapsed since the beginning of her last menstrual period).

Warnings about these dangers, together with FDA's own concerns about the safety of the abortion regimen, went unheeded. On September 28, 2000, FDA approved the new drug application ("NDA") for Mifeprex.[9] The initial reports of life-threatening and fatal adverse events appear to bear out the safety concerns underlying the pre-approval warnings. The Petition highlights a number of agency actions that were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. These serious departures from standard agency practice allowed the NDA for Mifeprex, a drug that is not safe for its intended use, to be approved by FDA.[10]

First, the approval of Mifeprex violated the legal requirements of FDA's Accelerated Approval Regulations found in Subpart H.[11] Mifeprex is not a drug for the treatment of a serious or life-threatening illness. It does not demonstrate the potential to address an unmet medical need because a less dangerous and more effective alternative for performing abortions already exists. It appears that FDA's decision to use Subpart H was motivated by its concern that, without restrictions, the drug could not be used safely. Rather than attempting to compensate for

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Ovulation for the small percentage of woman with a perfect 28 day cycle typically takes place between Days 12 and 14 and fertilization typically takes place 24 to 48 hours later.

[9] *See* U.S. Department of Health and Human Services, *HHS News*, Press Release P00-19, "FDA Approves Mifepristone for the Termination of Early Pregnancy," September 28, 2000. A selection of FDA documents relevant to its approval of Mifeprex may found at: <http://www.fda.gov/cder/drug/infopage/mifepristone>; and on a second page: <http://www.fda.gov/cder/foi/nda/2000/20687_mifepristone.htm>.

[10] FDA's unlawful approval of Mifeprex may not be unprecedented. The medical-scientific community and the mainstream press have called attention to a number of other instances in which one could question whether drugs and medical devices have been improperly approved. *See, e.g.*, Richard Horton, "Lotronex and the FDA: A Fatal Erosion of Integrity," *Lancet* 357 (May 19, 2001): 1544-1545; David Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times* (Dec. 20, 2000): at A1; Kit R. Roane, "Replacement Parts: How the FDA Allows Faulty, and Sometimes Dangerous, Medical Devices onto the Market," *U.S. News & World Report* (July 29, 2002): 54-59 (discussing FDA's recent approval policies regarding medical devices).

[11] 21 C.F.R. §§ 314.500-314.560. FDA's Accelerated Approval Regulations are set forth at 21 C.F.R. Part 314, Subpart H ("Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses") ("Accelerated Approval Regulations" or "Subpart H"). The Accelerated Approval Regulations were promulgated by FDA after notice and comment: New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234 (April 15, 1992) ("*Subpart H Proposed Rule*") and New Drug, Antibiotic, and Biological

the inherent dangerousness of Mifeprex by inappropriately resorting to the Subpart H approval mechanism, FDA should simply have refused to approve Mifeprex. (*See* Section III.D., *infra*.)

Second, Mifeprex was not proven to be "safe and effective" as required by law.[12] The scientific quality of the trials used to support the NDA was undeniably deficient according to Congress's statutory requirements and FDA's well-established standards.[13] The trials were not blinded, randomized, or concurrently controlled. FDA failed to explicitly waive its rules or offer a reasoned explanation for defying its own standards. (*See* Section III.E., *infra*.)

Third, the Mifeprex Regimen requires that Mifeprex be used in conjunction with another drug, misoprostol. FDA, however, has never approved misoprostol as an abortifacient. Although FDA normally opposes the promotion of off-label uses, in connection with the Mifeprex NDA, the agency sanctioned and itself participated in the promotion of the off-label use of misoprostol. Mifeprex, the label of which creates the false impression that misoprostol is approved for use as an abortifacient, is misbranded. (*See* Section III.F., *infra*.)

Fourth, and most critically, the Mifeprex Regimen is dangerous. FDA sought, without success, to convince the drug sponsor to place safety restrictions on Mifeprex. When that failed, on June 1, 2000, FDA itself proposed restrictions intended to reduce the unacceptable health risks associated with mifepristone abortions. Nevertheless, the agency, under concerted pressure from abortion advocates and politicians, ultimately approved mifepristone for use in a deregulated regimen that lacks key safeguards. For example, the regimen does not include a requirement that transvaginal ultrasound be used to date pregnancies and rule out ectopic

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Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942 (Dec. 11, 1992) ("*Subpart H Final Rule*") (available at: <http://www.fda.gov/cder/fedreg/fr19921211.txt>).

[12] *See* 21 U.S.C. § 355.

[13] *See* 21 C.F.R. § 314.126.

pregnancies, which cannot be treated with the Mifeprex Regimen. In addition, FDA failed to restrict access to mifepristone to physicians trained in the provision of Mifeprex and surgical abortions and capable of treating complications arising from abortions. Concerns about the dangers of Mifeprex were confirmed when Danco and FDA announced publicly on April 17, 2002, a number of serious adverse events, including two deaths. (*See* Section III.G., *infra*.)

Fifth, the drug's sponsor has neglected to require Mifeprex providers to adhere to the limited restrictions contained in the approved regimen. The sponsor's inaction is surprising in light of the fact that these restrictions are being flouted openly. Section 314.530 authorizes FDA to withdraw the approval of a Subpart H drug if a drug's sponsor does not fulfill its responsibility of ensuring compliance with the restrictions on the use of the drug. (*See* Section III.H., *infra*.)

Sixth, the safeguards employed in the U.S. Clinical Trial are not mirrored in the regimen that FDA approved. Transvaginal ultrasounds, for example, although employed in the U.S. Clinical Trial, are not required under FDA's approved regimen. Nor are the trial requirements governing emergency care reproduced in the approved regimen. (*See* Section III.I., *infra*.)

Seventh, FDA's waiver of its rule, 21 C.F.R. § 314.55, requiring the testing of all new drugs for their potential effects on children, has jeopardized the health and safety of American teenage girls who may have abortions. FDA expressly contemplated the pediatric use of Mifeprex, but waived, without an adequately reasoned justification, the requirement that the drug undergo pediatric testing. (*See* Section III.J., *infra*.)

Eighth, FDA did not require the sponsor of Mifeprex to honor its commitments for Phase IV studies, which provide the opportunity to study in-depth the drug's safety and effectiveness after approval. When FDA approved Mifeprex, the agency permitted the Population Council to replace the six Phase IV study commitments it had made in 1996 with two much narrower

commitments. The modified studies will not adequately address outstanding questions, such as the effects of mifepristone abortions on women outside the tested age range of 18 to 35 years. (*See* Section III.K., *infra*.)

In sum, FDA, in approving Mifeprex, acted in a manner inconsistent with its statutory authorization, regulations, and well-established policies. FDA did not provide a contemporaneous explanation of its numerous departures from past practice.[14] Its aberrant actions coupled with the absence of explanations violated a fundamental principle of administrative law; an agency must either adhere to prior policies or fully explain why it is not doing so.[15] The approval of Mifeprex was, therefore, arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. It must be reversed.

B. FDA APPROVAL OF THE MIFEPREX REGIMEN

1. The Introduction of Mifepristone into the United States

Roussel Uclaf, a French pharmaceutical firm, first developed and tested mifepristone ("RU-486") as an abortifacient. By April 1990 the drug had become permanently available in

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[14] An agency must explain its reasons for acting in a particular manner. *See, e.g., Securities & Exchange Commission v. Chenery Corp.*, 332 U.S. 194, 196-97 (1947) (noting that a court should not "be compelled to guess at the theory underlying the agency's action," but rather "[i]f the administrative action is to be tested by the basis upon which it purports to rest, that basis must be set forth with such clarity as to be understandable."). *Post hoc* rationalizations cannot salvage the agency's action with respect to Mifeprex. *See, e.g., Martin v. Occupational Safety and Health Review Commission*, 499 U.S. 144, 156-57 (1991) (*post hoc* rationalizations of counsel "do not constitute an exercise of the agency's delegated lawmaking powers"); *Investment Company Institute v. Camp*, 401 U.S. 617, 628 (1971) ("Congress has delegated to the administrative official and not to appellate counsel the responsibility for elaborating and enforcing statutory commands.").

[15] *See, e.g., Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970) ("[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute.") (footnote omitted) (citing approvingly *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 57 (1983)); *JSG Trading Corp. v. USDA*, 176 F.3d 535, 544 and 545 (D.C. Cir. 1999) (remanding agency action where "the agency manifestly failed to explain its abrupt departure from prior precedent" and noting that the agency "was obligated to articulate a principled rationale for departing from [its prior] test") (citations omitted); *Gilbert v. National Labor Relations Board*, 56 F.3d 1438, 1445 (D.C. Cir. 1995) ("It is, of course, elementary that an agency must conform to its prior decisions or explain the reason for its departure from such precedent.").

France. According to Dr. André Ulmann, the Roussel project manager for the development of RU-486, Roussel prohibited the commencement of any new studies in the United States and took the position that "under no circumstance[s]" would it permit a new drug application to be filed with FDA.[16] In fact, "the chairman of Hoechst [the parent company to Roussel] had officially declared that mifepristone was not compatible with the ethics of the company."[17]

Undeterred by Hoechst's reluctance to bring the drug to the United States, on January 22, 1993, President Clinton directed Department of Health and Human Services ("HHS") Secretary Donna Shalala to assess initiatives to promote the testing and licensing of mifepristone or other antiprogestins in the United States.[18] Further signaling that approval of mifepristone by FDA was a top priority of his Administration, President Clinton reportedly "wrote to Hoechst asking the company to file a new drug application with the FDA (an unprecedented situation in the pharmaceutical industry!), which Hoechst intransigently refused to do."[19]

In early 1993, Secretary Shalala and FDA Commissioner David Kessler "communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace."[20] On May 16, 1994, the Population Council reached an agreement with Roussel Uclaf, pursuant to which the European drug maker transferred "without remuneration,

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[16] *See* André Ulmann, M.D., "The Development of Mifepristone: A Pharmaceutical Drama in Three Acts," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 117-20, at 119. In 1994 Roussel Uclaf joined with the German pharmaceutical firm, Hoechst AG, to form Hoechst Roussel Ltd. In 1995, this entity merged with a third firm, Marion Merrell Dow, to form Hoechst Marion Roussel. In December 1999 Hoechst and Rhône-Poulenc combined to form Aventis, S.A., headquartered in Strasbourg, France.

[17] Ulmann, *infra* Appendix A, at 120.

[18] *See* Memorandum for the Secretary of Health and Human Services, "Importation of RU-486," *Public Papers of the Presidents: Administration of William J. Clinton, 1993* (Jan. 22, 1993) at 11.

[19] Ulmann, *infra* Appendix A, at 120 (emphasis in original).

[20] HHS Fact Sheet, "Mifepristone (RU-486): Brief Overview," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

its United States patent rights for mifepristone (RU-486) to the Population Council . . . ."[21] Secretary Shalala was instrumental in bringing about the transfer of the patent rights to the Population Council[22] and even set a deadline – May 15, 1994 – for the transfer.[23]

After obtaining the American patent rights to mifepristone, the Population Council conducted clinical trials in the United States and filed a new drug application in 1996. The Population Council established a non-profit corporation, American Health Technologies ("AHT"), to assist in the effort to bring the drug to the market.[24] The Population Council ultimately granted Danco Laboratories, LLC ("Danco"), which was incorporated in the Cayman Islands in 1995, "an exclusive license to manufacture, market, and distribute Mifeprex in the United States."[25] Danco, after a difficult search,[26] selected the Chinese drug manufacturer,

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[21] HHS Press Release, "Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

[22] *Id.* ("Shalala commended Roussel Uclaf and the Population Council for coming to closure after months of complex negotiations amid repeated urging from the Clinton administration.")

[23] *See* William J. Eaton, "Path Cleared for Abortion Pill Use Medicine: French Maker of RU-486 Gives Patent Rights to a Nonprofit Group," *Los Angeles Times*, May 17, 1994, at A1 ("Negotiations between the French manufacturer and the Population Council dragged on for more than a year until Shalala set a May 15 deadline, producing the agreement . . . .").

[24] Dr. Susan Allen, who once served as president and CEO of American Health Technologies, joined the staff of the Reproductive and Urologic Drug Products Division in FDA's Center for Drug Evaluation and Research in 1998 as a medical officer and was promoted to team leader for reproductive drugs in January 1999. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14. Dr. Allen became acting director of the Division in January 2000 and permanent director on June 18, 2000. *See id. The Pink Sheet* also commented, "Allen is presumably recused from the mifepristone review as a result of her prior experience with the product." *Id.*

[25] Danco, "The History of Mifeprex,"available at <http://www.earlyoptionpill.com/history.php3>. (Danco has dubbed mifepristone "the Early Option Pill" for marketing purposes.) Little information about Danco is available. *See* Robert O'Harrow, "RU-486 Marketer Remains Elusive," *Washington Post* (Oct. 12, 2000): at A18 ("Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry."). Danco is apparently a successor entity to Advanced Health Technology. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14 (reporting that Advanced Health Technologies had become Neogen, which, in turn, had become Danco, according to the Population Council and Danco, "with some management and investor changes").

[26] In 1995 Danco contracted with a Hungarian pharmaceutical firm, Gideon Richter, to manufacture mifepristone for American distribution. After Gideon Richter reneged on the contract in February 1997, Danco sued Gideon Richter for breach of contract and began searching for a new producer. *See* "Ru-486: U.S. Partners Sue European Manufacturer," *Kaiser Daily Reproductive Health Report* (June 12, 1997) (available at: <http://www.kaisernetwork.org/reports/1997/06/a970612.1.html>). This was one of a number of lawsuits stemming

Shanghai Hua Lin Pharmaceutical Company, to manufacture the drug.[27] Abortion advocates eagerly awaited the approval of mifepristone in the United States because, among other reasons, they anticipated that it would enhance women's access to abortion.[28]

2. FDA Approval of Mifepristone

The Population Council filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.[29] FDA initially accorded the drug standard review, but in a letter dated May 7, 1996, FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.[30] On September 18, 1996, FDA issued a letter

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from attempts to bring mifepristone to the United States. *See* "Ru-486: Litigation Could Cause Delay For U.S. Introduction," *Kaiser Daily Reproductive Health Report* (Dec. 17, 1996) (available at: <http://www.kaisernetwork.org/reports/1996/12/a961217.9.html>) (describing some of the legal problems encountered by the Population Council in bringing the drug to market).

[27] Pamela Wiley, "Chinese Plant to Make RU-486 for U.S.," (Oct. 15, 2000) (available at: <http://www.nurseweek.com/news/00-10/1015-486.asp>).

[28] *See* Margaret Talbot, "The Little White Bombshell," *New York Times Magazine* (July 11, 1999): at 39-43 ("'One of my real, and I think realistic, hopes for this method,' says Carolyn Westhoff, an OB-GYN at Columbia University medical school who offers medical abortion as part of a clinical trial, 'is that it will help get abortion back into the medical mainstream and out of this ghettoized place it's been in.' And if that is indeed the scenario we're looking at – a scenario in which abortion is folded far more seamlessly into regular medical practice – then it has implications not only for women's experience of abortion but for the politics of abortion as well."); *id.* ("Not only are mifepristone abortions, by nature, more discreet than their surgical equivalents (like vacuum aspiration), but the practitioners who prescribe them will almost certainly constitute a larger and a more varied group than the dwindling corps of OB-GYNs willing to do surgical abortions.") In fact, access to medical abortion, will continue to depend on the availability of surgical abortion, which serves as a back-up in FDA's approved Mifeprex regimen. Thus, it is spurious to suggest that Mifprex abortions can safely be made available in places in which surgical abortion is not offered.

[29] The application was dated March 14, 1996 and received by FDA on March 18, 1996. *See* Letter, FDA/CDER to Ann Robbins, Population Council (Sept. 18, 1996): at 1 ("1996 Mifepristone Approvable Letter").

[30] *See* Letter, FDA/CDER to Ann Robins, Population Council (May 7, 1996)[FDA FOIA Release: MIF 006431]. The Population Council filed its complete response on March 30, 2000, which gave FDA until September 30, 2000 to act on the application. In fiscal year 2000 a "standard" designation would have given FDA at least ten months to consider the application. FDA accorded mifepristone "priority review," which typically required FDA to act within six months. *See* FDA/CDER, "PDUFA Reauthorization Performance Goals and Procedures" (Nov. 16, 1997) (available at: <http://www.fda.gov/cder/news/pdufagoals.htm>) ("Fiscal Year 2000"). Of 98 approvals in 2000, only 20 were Priority Review drugs. *See* FDA/CDER, *Report to the Nation* (2000): at 6. FDA's use of priority review appears inappropriate when considered in light of the agency's current guidance on the issue, which states that priority review is appropriate when "[t]he drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease." *See* FDA/CDER, "Review Management: Priority Review Policy," Manual of Policies and Procedures (MAPP) 6020.3, at 1 (Apr. 22, 1996) (text bracketed as in original).

stating that the application was approvable and requested more information from the sponsor.[31] FDA issued a second approvable letter for mifepristone, dated February 18, 2000, setting forth the remaining prerequisites for approval.[32] The 2000 Mifepristone Approvable Letter announced that FDA had "considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[33]

On September 28, 2000, FDA approved mifepristone ("Mifeprex™") "for the medical termination of intrauterine pregnancies through 49 days' pregnancy."[34] Mifeprex was approved under Subpart H, which, FDA explained, "applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with certain skills or experience."[35] The approved regimen requires at least three office visits.[36] FDA required the Population Council to include, on the Mifeprex Label, a "black box warning for special problems, particularly those that may lead to death or serious injury."[37]

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[31] 1996 Mifepristone Approvable Letter at 1.

[32] 2000 Mifepristone Approvable Letter at 1.

[33] 2000 Mifepristone Approvable Letter at 5.

[34] Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 1 ("Mifeprex Approval Letter"). In conjunction with the Mifeprex Approval Letter, FDA issued a memorandum that expanded upon the basis for and the restrictions on the approval of Mifeprex. *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 6 ("Mifeprex Approval Memo").

[35] Mifeprex Approval Memo at 6.

[36] Pursuant to the approved regimen, on "Day One: Mifeprex Administration" the patient reads the Medication Guide, signs the Patient Agreement, and ingests 600 mg of Mifeprex; on "Day Three: Misoprostol Administration" the patient ingests 400 micrograms of misoprostol orally (unless abortion has occurred and been confirmed by clinical examination or ultrasonographic scan); and, on or about "Day 14: Post-Treatment Examination" the patient returns to the practitioner for verification through a clinical examination or ultrasound that the pregnancy has been successfully terminated. *See* Mifeprex Label ("Dosage and Administration")(available at: <http://www.fda.gov/cder/foi/label/2000/20687lbl.pdf>).

[37] Mifeprex Approval Memo at 2 (citing 21 CFR 201.57(e), which authorizes FDA to require such a warning). The terms "label," "labeling," and "package insert" are often used interchangeably in food and drug law literature. In this Petition, "Label" describes the fine-print "package insert" that accompanies a drug when it is purchased. However, the FD&C Act defines "label" as "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." 21 U.S.C. § 321(k). The term "labeling," which will also appears in this Petition,

FDA also outlined the Population Council's post-approval, Phase IV study commitments[38] and waived, without explanation, FDA's regulations providing that all new drugs must be tested for safety and effectiveness in children.[39]

C. BACKGROUND ON FDA'S DRUG APPROVAL PROCESS

1. FDA's Default Rules for Establishing Drug Safety and Effectiveness

FDA's regulations state that "[t]he purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[40] FDA's default criteria for establishing safety and effectiveness are commonly referred to as the agency's "gold standard."[41] At the core of this default standard is FDA's recognition, reflecting the development of the scientific method and its application to pharmacology, that human bias and misperceptions are pervasive and that every precaution must be taken to avoid them. "The history of experimental medicine and research psychology," Michael Greenberg writes, "had demonstrated that uncontrolled, unblinded clinical trials were systematically vulnerable to experimenter bias, placebo effects, and the like."[42] Consequently, rigorous policies have been set forth by FDA and,

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encompasses "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). "Labeling" may even describe promotional materials used by the drug manufacturer including "[b]rochures, booklets, mailing pieces, . . . price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, . . . and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses . . . ." 21 C.F.R. § 202.1(l)(2). FDA has provided more information on this terminology at: <http://www.fda.gov/cder/handbook/adverdef.htm>.

[38] *See* Mifeprex Approval Memo at 7.

[39] *See* FDA Mifeprex Approval Letter at 3.

[40] 21 C.F.R. § 314.126(a).

[41] *See* Jennifer Kulynych, "Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 127-149, at 129. We will refer to these criteria as the "default standard."

[42] Michael D. Greenberg, "AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process," *Legislation and Public Policy* 3 (2000): 295-350, at 308.

more recently, by the International Conference on Harmonisation ("ICH") to eliminate bias from the evaluation of drug safety and effectiveness.[43]

FDA has been criticized for its zealous implementation of this policy,[44] but there is widespread recognition of the value of the default standard. The 1962 statutory amendments to the FD&C Act "authorized the agency to review all NDAs, not only to assess drug safety, but also to determine whether a manufacturer has provided 'substantial evidence' from 'adequate and well-controlled investigations' that a drug is effective for its intended use."[45] In implementing regulations, FDA "required that the evidence include at least one (and usually two) well-controlled (preferably 'blind') trials showing statistically significant results for treatment of humans with the new drug."[46] "[B]arring unusual circumstances, the agency ordinarily requires two successful and well-controlled clinical trials for new drug approval."[47] FDA's mandate for clinical trials "has two very important elements:"

> (1) a "controlled" trial, in which an experimental drug is compared to a placebo, or a known effective treatment in order to establish the comparative efficacy of the drug, and
> (2) a "double-blind" trial, which involves random assignment of research subjects to the

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[43] 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 homepage, (www.ich.org), for the ICH describes the organization as follows: "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 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."

[44] *See, e.g.*, Henry I. Miller, "Failed FDA Reform," *Regulation* 21 (Summer 1998): 24-30.

[45] Kulynych, *infra* Appendix A, at 129 (citing 21 U.S.C. § 355(d)).

[46] Greenberg, *infra* Appendix A, at 307 (citing 21 C.F.R. § 314.126 (1999). FDA comprehensively revised NDA evaluation rules in what is commonly referred to as the "NDA Rewrite." *See Final Rule*, "New Drug and Antibiotic Regulations," 50 Fed. Reg. 7452 (Feb. 22, 1985). Section 314.126 was promulgated in that final rule. *Id.* at 7506-7.

[47] Kulynych, *infra* Appendix A, at 130.

experimental and control groups, under conditions in which neither the doctors nor the research subjects know who is getting the experimental drug and who the control.[48]

Each of the mandated features helps to eliminate bias in trial results. First, in "double-blinded" studies neither the patient nor the provider team (physician, nurse, etc.) knows the identity of the drug administered. If that is not possible, the person evaluating the trial results will not know which treatment has been administered to which subject. Second, a "randomized" study requires a random determination of which subject receives which treatment. This determination is often effected through computer-generated assignments done before clinical testing begins. Finally, comparison-control (also known as "comparator-control") requires that the experimental drug be compared *concurrently* to the current best treatment, or, alternatively, to a placebo. A placebo is used when the drug being tested represents the first treatment of its kind for the particular indication and no established treatment exists.

2. FDA Initiatives to Expedite the Approval of Drugs for the Very Sick

Largely in response to FDA's perceived slowness in approving drugs for human immunodeficiency virus ("HIV") patients, the agency undertook several initiatives to either expedite the ability of seriously or terminally-ill patients to have access to experimental drugs or to provide processes "intended to move drugs to market more quickly by compressing clinical development and FDA review times."[49] In 1988, FDA adopted an interim rule establishing Subpart E of 21 C.F.R. Part 312 ("Drugs Intended to Treat Life-Threatening and Severely-

[48] Greenberg, *infra* Appendix A, at 307-8 (footnotes omitted).

[49] Sheila R. Shulman and Jeffrey S. Brown, "The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?" *Food and Drug Law Journal* 50 (1995): 503-531, at 503-4.

Debilitating Diseases").[50] Subpart E embodied several of the new procedures that FDA had used to bring the HIV medication, AZT (zidovudine), to market quickly.[51] Subpart E also created a "collaborative framework in which early and repeated consultation between the FDA and pharmaceutical manufacturers served to facilitate clinical trials, and to insure ex ante that prospective research designs would meet with subsequent regulatory approval."[52] "Taken together," the innovations found in Subpart E, "served to radically alter the new drug approval process with regard to life-threatening illnesses, particularly for AIDS."[53]

On April 15, 1992, FDA took its procedural innovations further when it proposed an "Accelerated Approval" process (*i.e.*, Subpart H). Shulman and Brown believe that Subpart H "represent[ed] the most significant departure from the traditional FDA standards for drug approval."[54] Subpart H's "major point of departure" from previously existing approval regimes was its focus on granting drug approval "on the basis of the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit over time."[55] A "surrogate end point" or "surrogate marker" is "a laboratory parameter or physical sign that is used in a clinical trial as a substitute for a clinically meaningful end point, such as mortality."[56] The value of surrogate

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[50] *See Interim Rule*, "Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses," 53 Fed. Reg. 41,516 (Oct. 21, 1988). The Subpart E rules may be found at 21 C.F.R. §§ 312.80-88.

[51] *See* Greenberg, *infra* Appendix A, at 321.

[52] Greenberg, *infra* Appendix A, at 321 (citation omitted).

[53] Greenberg, *infra* Appendix A, at 323.

[54] Shulman and Brown, *infra* Appendix A, at 514.

[55] Shulman and Brown, *infra* Appendix A, at 514. Likewise, Greenberg observed that the "essential element of the accelerated approval regulations [*i.e.*, Subpart H] was the provision that 'surrogate endpoints' could be employed as the empirical basis for FDA approval of a new drug." Greenberg, *infra* Appendix A, at 323 (citation omitted).

[56] Dennis F. Thompson, "Surrogate End Points, Skepticism, and the CAST Study," editorial, *Annals of Pharmacotherapy*, 36 (Jan. 2002): 170-71, at 170 (citations omitted).

endpoints lies in their ability to predict clinical outcomes.[57] As "examples of surrogate end points that have been proven to be excellent predictors of clinical outcomes and, hence, have saved both money and precious time expediting drugs to the patient care arena," Dean Dennis Thompson cites "a diverse group of antihypertensive drugs approved on the basis of reduced blood pressure effects [that] has shown clear benefits in reducing cardiovascular events and mortality."[58] With the passage of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Congress effectively codified Section 314.510, the surrogate endpoint provision of Subpart H.[59]

Neither Shulman and Brown nor Greenberg focused on a second type of drug approval included in Subpart H – codified now at 21 C.F.R. § 314.520.[60] This second avenue for Subpart H approval is reserved for circumstances in which "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted."[61] Pursuant to this provision "FDA may approve a treatment subject to special

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[57] *See* Thompson, *infra* Appendix A, at 170.

[58] Thompson, *infra* Appendix A, at 170.

[59] This codification was part of Congress's major reauthorization and modernization of the Federal Food, Drug & Cosmetic Act. Section 506(b) of FDAMA (21 U.S.C. § 356) "in effect, codifie[d] in statute FDA's Accelerated Approval Rule . . . , made final in 1992, which allows expedited marketing of certain new drugs or biological products intended to treat serious or life-threatening illnesses and that appear to provide meaningful therapeutic benefits to patients compared with existing treatments." FDA Centers for Drug Evaluation and Research and for Biologics Evaluation and Research, *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*, at 2 (Sept. 1998) (footnote omitted). While clearly codifying Subpart H's surrogate endpoint provision at 21 U.S.C. § 356(b)(1), Congress does not appear to have enacted a parallel provision to Section 314.520, which pertains to "restricted use" drugs, under which Mifeprex was approved.

[60] Section 314.520 (Approval with restrictions to ensure safe use.) states:

> (a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, such as:
> (1) Distribution restricted to certain facilities or physicians with special training or experience; or
> (2) Distribution conditioned on the performance of specified medical procedures.
> (b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

[61] *Subpart H Final Rule*, 57 Fed. Reg. at 58942.

distribution or use restrictions that address outstanding safety issues."[62] Section 314.520 balanced FDA's desire to bring clinically beneficial drugs to the market with the agency's concern that "[s]ome drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use."[63] The agency explained "that some clinically beneficial drugs can be used safely only if distribution and use are modified and restricted."[64]

Section 314.520 is intended for drugs that are vitally necessary, but which may impose greater than normal risks for the patient.[65] FDA was willing "to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to counterbalance the known safety concerns."[66] Postmarketing restrictions would be designed "to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction."[67] FDA intended to employ restrictions on distribution "only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will *not* assure the product's safe use."[68] In the absence of restrictions, which "may vary with the circumstances of each drug[,] . . . the drug would be adulterated under Section 501 of the act, misbranded under Section 502 of the act, or not shown to be safe under Section 505 of the act."[69] In short, "[w]ithout such restrictions, the drugs would not meet the statutory criteria,

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[62] Geoffrey M. Levitt, James N. Czaban, and Andrea S. Paterson, "Chapter 6: Human Drug Regulation" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 200.

[63] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[64] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[65] Of course, "[v]irtually all drug[s] can be toxic to humans, and no drug is completely free of risk," but, as the seriousness of an illness and the effect of the drug on that illness increase, "the greater the acceptable risk from the drug." *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[66] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

[67] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[68] *Subpart H Final Rule*, 57 Fed. Reg. at 58952 (emphasis added).

[69] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

could not be approved for distribution, and would not be available for prescribing or dispensing."[70] Mifeprex was the third of four drugs approved pursuant to Section 314.520.[71]

D. FDA'S APPROVAL OF MIFEPREX UNDER ITS ACCELERATED APPROVAL REGULATIONS (SUBPART H) WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

FDA's accelerated approval regulations (Subpart H) apply to certain new drug products "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[72] When it proposed Subpart H in 1992, FDA observed that the following types of illness would fall within the reach of Subpart H:

> The terms "serious" and "life-threatening" would be used as FDA has defined them in the past. The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel disease,

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[70] *Subpart H Final Rule*, 57 Fed. Reg. at 58951. The agency continued: "The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing." *Id.* at 58951-52.

[71] On June 7, 2002, the drug Lotronex (alosetron hydrochloride) was reintroduced to the market after a *Supplemental* NDA was approved pursuant to Subpart H's redistricted distribution provision. *See* Letter, FDA/CDER, Florence Houn, M.D., Director, Office of Drug Evaluation III to Olivia Pinkett, Product Director, Regulatory Affairs, GlaxoSmithKline (June 7, 2002): at 1 ("This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program. . . . You have indicated your agreement with approval under restricted conditions.").

[72] 21 C.F.R. § 314.500. The rule was amended in 1999 to remove the words "and antibiotic." *See* Conforming Regulations Regarding Removal of Section 507 of the Federal Food, Drug, and Cosmetic Act, *Final Rule*, 64 Fed. Reg. 396, 402 (Jan. 5, 1999).

> asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, psychoses, and many other diseases can be serious for certain populations or in some or all of their phases.[73]

According to FDA, the agency has approved 38 NDAs, including the Mifeprex application, under Subpart H.[74] Of these approvals, 20 were for the treatment of HIV and HIV-related diseases, nine were for the treatment of various cancers and their symptoms, four were for severe bacterial infections, one was for erythema nodosum leprosum (leprosy), one was for hypotension, and, finally, one was for the termination of unwanted pregnancies.[75]

Pregnancy, without major complications, is not a "serious or life-threatening illness" for purposes of Subpart H. It is, rather, a normal physiological state experienced by most females one or more times during their childbearing years, and it is rarely accompanied by complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability. Thus, pregnancy is not the kind of exceptional circumstance that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point.

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[73] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13235. In the *Subpart H Final Rule*, FDA asserted that "serious and life-threatening illnesses" would be readily identifiable: "FDA discussed the meaning of the terms 'serious' and 'life-threatening' in its final rules on 'treatment IND's' (52 FR 19466 at 19467, May 22, 1987) and 'subpart E' procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every 'serious' and 'life-threatening' disease that would be within the scope of this rule. In FDA's experience with 'treatment IND's' and drugs covered by the 'subpart E' procedures there have not been problems in determining which diseases fall within the meaning of the terms 'serious' and 'life-threatening,' and FDA would expect no problems under this accelerated approval program." *Subpart H Final Rule*, 57 Fed. Reg. at 58945.

[74] These estimates are based on the version of FDA's webpage, dated February 5, 2002, listing Subpart H approvals, *infra* Appendix A.

[75] *See* FDA/CDER webpage, "NDAs Approved under Subpart H," *infra* Appendix A. A copy of the most recently available version is reproduced in Appendix C (available at: <http://www.fda.gov/cder/rdmt/accapp.htm>). *See also* "NDA Supplements Approved under Subpart H" (available at: <http://www.fda.gov/cder/rdmt/accappr1.htm>) (supplemental approvals are not included in the figures set forth in the text because they refer to FDA actions regarding drugs that have already been approved).

In fact, the Population Council argued strenuously that its application for mifepristone did not fall within the scope of Subpart H.[76] In a letter to FDA written approximately three weeks before the final approval of the mifepristone NDA, the Population Council's Sandra P. Arnold protested, ". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."[77] Arnold argued correctly that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."[78] She continued, stating, "Neither is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."[79] In the next paragraph, after directly quoting the *Supbart H Final Rule*, Ms. Arnold asserted that "[t]he plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."[80] She added that, unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."[81] She continued that, "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."[82]

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[76] The Population Council appears to have been concerned about getting the drug approved "without invoking the Subpart H regulatory provisions that signal 'big deal' to the pharmaceutical industry." Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 4 [FDA FOIA Release: MIF 001333-49]("Sandra Arnold Letter"). Sandra Arnold was "Vice President, Corporate Affairs" of the Population Council.

[77] Sandra Arnold Letter at 1.

[78] Sandra Arnold Letter at 1-2.

[79] Sandra Arnold Letter at 2.

[80] Sandra Arnold Letter at 2.

[81] Sandra Arnold Letter at 2.

[82] Sandra Arnold Letter at 2. Ms. Arnold also warned the agency that extending the scope of Subpart H to include pregnancy and unwanted pregnancy by exercising agency "judgment" was not defensible; the exercise of such judgment should go to whether or not "a particular disease actually is serious, not [act as] a means of stretching the meaning of serious to cover entirely new categories of non-serious situations." *Id.*

Additionally, Mifeprex fails to meet the second requirement set forth in Section 314.500 that drugs approved under Subpart H "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.)" As was noted above, the Mifeprex Approval Memo contends "that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H [and] [t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[83] By defining the "therapeutic benefit" solely as the avoidance of the current standard of care's delivery mechanism, FDA effectively guarantees that a drug will satisfy this second prong of Subpart H as long as it represents a different method of therapy.[84] It does not appear that such considerations formed the basis of any other Subpart H approval.

When FDA adopted Subpart H, it cited as "readily understood illustrations of the intent of the [meaningful therapeutic benefit] requirement" an "improved response compared to available therapy" and the "ability to treat unresponsive or intolerant patients."[85] Based on these illustrations, Mifeprex does not fall within the intent of the requirement. First, there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions. Dr. Jeffrey Jensen conducted a study to compare the safety and

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[83] Mifeprex Approval Memo at 6.

[84] The view that merely making a different mode of therapy available *per se* produces a benefit is inconsistent with the position the agency has articulated elsewhere. MAPP 6020.3, which defines eligibility for FDA priority review, suggests that drug therapies are not inherently superior to non-drug therapies. Specifically, a drug may be afforded priority review if it would provide a significant improvement when compared with "marketed products . . . including non-"drug" products/therapies." *See* FDA/CDER, "Review Management: Priority Review Policy," MAPP 6020.3, at 1 (Apr. 22, 1996).

[85] *Subpart H Final Rule*, 57 Fed. Reg. at 58947.

efficacy of medical abortion with that of surgical abortion.[86] The study compared 178 patients who, as participants in the U.S. clinical trial in support of the Mifeprex NDA, underwent mifepristone/misoprostol abortions, with 199 patients who later received surgical abortions at the same clinical site. The primary procedure failed (*i.e.*, there was a subsequent surgical intervention) in 18.3 percent of the mifepristone/misoprostol patients and 4.7 percent of the surgical patients.[87] Of the mifepristone/misoprostol patients who failed their primary procedure, 12.5 percent required surgical intervention for acute bleeding, 43.8 percent for persistent bleeding, 15.6 percent for incomplete abortion, and 28.1 percent for ongoing pregnancy.[88] By contrast, the sole cause for surgical intervention among the surgical patients who failed their primary procedure was persistent bleeding.[89] In addition, mifepristone/misoprostol patients "reported significantly longer bleeding" and "significantly higher levels of pain . . . , nausea . . . , vomiting . . . , and diarrhea" than their surgical counterparts.[90]

Second, Mifeprex does not treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion. To the contrary, because "medical abortion failures should be managed with surgical termination" the option for surgical abortion must be available for any Mifeprex patient.[91] As the U.S. trial conducted in support of the NDA indicated, the possibility

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[86] Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study," *Contraception* 59 (1999): 153-159 ("Jensen Study")[FDA FOIA Release: MIF 000438-44].

[87] *See* Jensen Study, *infra* Appendix A, at 155, Table 2.

[88] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[89] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[90] Jensen Study, *infra* Appendix A, at 156.

[91] Mifeprex Label ("Warnings").

for failure is substantial.[92] Thus, any patient who would be intolerant of surgical abortion, if such a class of patients exists, cannot use the Mifeprex Regimen.

As discussed below, FDA approved Mifeprex pursuant to Section 314.520 in order to impose safety restrictions to counteract the risks it had identified. FDA, confronted by the sponsor's refusal to establish voluntary restrictions on distribution,[93] viewed Subpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe.[94] The inappropriate application of Section 314.520 served the agency's immediate need of conditioning the drug's approval on certain safety measures. However, Mifeprex fails to satisfy the Subpart H requirements because, although it presents great risk to the user, it neither treats a serious or life-threatening illness nor provides a therapeutic benefit above existing treatments. A drug with such characteristics should not have been approved.

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[92] 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," at 11 (Table 1) (reporting a failure rate of 8% for pregnancies less than or equal to 49 days' duration) ("Medical Officer's Review").

[93] Early in the approval process, FDA anticipated that the Population Council would cooperate, thus obviating the need for Subpart H restrictions: "[B]ecause the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted." *See* Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62]. The voluntary restrictions placed on the drug Accutane, a drug for severe acne, illustrate that a cooperative drug sponsor may be able to obviate the need for Subpart H restrictions. Because Accutane can cause birth defects, the restrictions are designed to ensure that women taking the drug are not and do not become pregnant. The "System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™)," controls the distribution of the drug through the issuance of yellow Accutane Qualification Stickers. These stickers are distributed to physicians who meet a number of qualifications and they, in turn, distribute them to patients, who must undergo two tests to confirm they are not pregnant and must commit to use two forms of contraception. Pharmacists may fill prescriptions for the drug only if they bear the qualification sticker, were issued within the past week, and prescribe no more than 30 days' worth of the drug. *See* Accutane Label.

[94] This interpretation of the agency's actions is supported by FDA spokeswoman Crystal Rice, who said "that outside of Subpart H, the FDA does not have another regulatory program to mandate safety restrictions on drug marketing for drugs used to treat 'serious or life-threatening illnesses'" and "that 'other agreements [or restrictions on the drug] not under Subpart H worked out between FDA and a sponsor would be essentially voluntary.'" "Danco Medical Director Explains Mifepristone's FDA Approval Not Fast-Tracked or Accelerated, Despite Media Reports," *Kaiser Daily Reproductive Health Report* (March 29, 2001) (available at: <http://report.kff.org/archive/repro/2001/3/kr010329.5.htm>).

E. THE CLINICAL TRIALS DID NOT PRESENT "SUBSTANTIAL EVIDENCE" THAT THE MIFEPREX REGIMEN IS SAFE AND EFFECTIVE

FDA's approval of the Mifeprex NDA ran counter to Congress's statutory requirements, the agency's regulations and guidance documents, and FDA's well-established standards for the quality and quantity of scientific evidence needed to support an agency finding that a new drug is safe and effective. The clinical trials submitted by the Population Council to support its NDA did not use the full set of design features FDA typically requires to produce unbiased investigations of drug safety and effectiveness. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex Regimen. Inexplicably, FDA failed to perform a statistical analysis of the data from the American trial. Furthermore, FDA's approval of Mifeprex pursuant to Subpart H compounds the deficiencies in the trials because sponsors of Subpart H drugs must demonstrate that the drug for which approval is being sought provides a "meaningful therapeutic benefit over existing therapy." Because Mifeprex was approved in reliance on French and American trials that did not compare the Mifeprex Regimen with the existing standard of care for ending pregnancies (*i.e.*, surgical abortion), the trials cannot support this Subpart H approval.

1. The Clinical Trials Underlying FDA's Approval of Mifeprex

FDA based its approval of Mifeprex on safety and effectiveness data derived from two French clinical trials ("French Clinical Trials") and one U.S. clinical trial ("U.S. Clinical Trial").[95] Neither the French Clinical Trials nor the U.S. Clinical Trial was blinded, randomized,

[95] *See* Mifeprex Approval Memo, *infra* Appendix A, at 1.

or concurrently controlled – the hallmarks of unbiased, scientific analysis generally relied upon by FDA.

a. The French Clinical Trials

The French Clinical Trials, which formed the basis for the Population Council's original NDA submission in 1996, were open-label, multi-center studies.[96] One of these trials consisted of 1,286 patients at 24 centers in France ("French Trial I").[97] The trial was limited to women who had pregnancies of no more than 49 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[98] On the first day of the procedure, the patient received 600 mg of mifepristone orally "in the presence of a study investigator."[99] Approximately 48 hours later, she returned and, unless the abortion had already taken place, ingested 400 micrograms of misoprostol "in the presence of a study investigator."[100] The patient remained under observation for four hours or more after the ingestion of misoprostol and returned for "a final assessment of the pregnancy termination procedure" eight to 15 days later.[101]

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[96] FDA's Reproductive Health Drugs Advisory Committee ("FDA Advisory Committee"), which met in July 1996 to consider the mifepristone NDA, based its conclusion primarily on the French trial along with preliminary data from the U.S. Clinical Trial. *See* FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 6, 132-33 (July 19, 1996) (*FDA Hearings Transcript*)[FDA FOIA Release: MIF 005200-90]. Committee member Dr. Mary Jo O'Sullivan asked why the Committee meeting was being held "at this time when the data is not finalized." *Id.* at 37. Dr. C. Wayne Bardin, who was responsible for overseeing the Population Council's NDA preparation, responded that "we have sufficient data . . . [f]rom the non-U.S. data to allow us to submit an application to the FDA." *Id.*

[97] *See* FDA, Statistical Review and Evaluation, at 2-4 (May 21, 1996) ("Statistical Review"). This French trial is referred to as FFR/91/486/14.

[98] *See* Statistical Review, *infra* Appendix A, at 2. "Since the ultrasound estimate of gestational age was more reliable than the patient's estimate . . . gestational age based on the ultrasound examination was used if available." *Id.* Investigators, in violation of study protocol, included some women with pregnancies of more than 49 days. *See* Statistical Review, *infra* Appendix A, at 3.

[99] *See* Statistical Review, *infra* Appendix A, at 2.

[100] *See* Statistical Review, *infra* Appendix A, at 2.

[101] *See* Statistical Review, *infra* Appendix A, at 2.

The efficacy analysis of French Trial I encompassed only 1,205 patients, while the safety analysis included all 1,286 participants.[102] The regimen resulted in "complete expulsion" in 95.4 percent of the 1,189 participants whose pregnancies were 49 days or less.[103] The rate of complete expulsion declined with increased gestational age.[104] Sixty-one women had complete expulsions before taking misoprostol.[105] Almost 86 percent of patients in French Trial I experienced at least one adverse event as a result of the procedure.[106]

The second French clinical trial ("French Trial II") enrolled 1,194 patients at 11 centers.[107] The trial was limited to women who had pregnancies of no more than 63 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[108] The regimen used in French Study II was essentially the same as that described above in connection with French Study I, except that an additional 200 micrograms of misoprostol was administered if complete expulsion did not occur within three hours after taking the initial 400 microgram dose of misoprostol.[109] Patients who received the second dose of misoprostol remained under observation for a total of five hours.[110]

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[102] *See* Statistical Review, *infra* Appendix A, at 3.

[103] *See* Statistical Review, *infra* Appendix A, at 3. Patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (2.8%), ongoing pregnancies (1.5%), and those who needed surgical procedures for bleeding (.3%) were classified as failures. *See id.* at 3 and 9 (Table 1).

[104] *See* Statistical Review, *infra* Appendix A, at 3 ("[T]here was a statistically significant . . . inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.").

[105] *See* Statistical Review, *infra* Appendix A, at 3. Twenty-six of these women received misoprostol anyway, because the investigators did not realize that they had had complete abortions. *See id.*

[106] *See* Statistical Review, *infra* Appendix A, at 4.

[107] *See* Statistical Review, *infra* Appendix A, at 4-7. This French trial is designated as FF/92/486/24.

[108] *See* Statistical Review, *infra* Appendix A, at 4-5.

[109] *See* Statistical Review, *infra* Appendix A, at 5.

[110] *See* Statistical Review, *infra* Appendix A, at 5.

The efficacy analysis of French Trial II encompassed only 1,104 patients, while the safety analysis included all 1,194 participants.[111] The regimen resulted in "complete expulsion" in 92.8 percent of the participants.[112] The rate of complete expulsion declined with increased gestational age.[113] Twenty-six women had complete expulsions before taking misoprostol.[114] Almost 93 percent of paticnts in French Trial II experienced at least one adverse event as a result of the procedure.[115]

Among the deficiencies that characterized both French Clinical Trials was the absence of an appropriate control group. Consequently, as an FDA statistician concluded after reviewing the data from the French Clinical Trials: "In 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."[116]

b. The U.S Clinical Trial

The U.S. Clinical Trial was carried out from September 13, 1994 to September 12, 1995 at various qualified university hospitals and clinics.[117] Patients had to satisfy a number of criteria

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[111] *See* Statistical Review, *infra* Appendix A, at 5.

[112] *See* Statistical Review, *infra* Appendix A, at 6. As in French Study I, patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (4.0%), ongoing pregnancies (2.3%), and those who needed surgical procedures for bleeding (.9%) were classified as failures. *See id.* at 5 and 12 (Table 4).

[113] *See* Statistical Review, *infra* Appendix A, at 6.

[114] *See* Statistical Review, *infra* Appendix A, at 6.

[115] *See* Statistical Review, *infra* Appendix A, at 7.

[116] Statistical Review, *infra* Appendix A, at 7-8.

[117] *See* Medical Officer's Review, *infra* Appendix A, at 6. More specifically, the U.S. Clinical Trial consisted of "two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols." Medical Officer's Review, *infra* Appendix A, at 6 and 9. In this Petition, the trials will be referred to as "the U.S. Clinical Trial," because the protocols employed were identical, the results of the two trials were analyzed jointly, and the results were published in the same article. *See* Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri

to be included in the study.[118] All patients were screened by pelvic examination and ultrasound to ensure that their pregnancies were not too advanced for the procedure.[119] On their first visit, patients took 200 mg of mifepristone orally "[i]n the presence of the investigator."[120] Patients returned 36 to 60 hours later to ingest 400 micrograms of misoprostol orally in the presence of the investigator, unless the investigator determined that the termination was already complete.[121] Following ingestion of misoprostol, patients were observed for a minimum of four hours.[122] Patients were instructed to return again 12 days later for a follow-up assessment.[123] A patient's pregnancy was terminated surgically "at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion."[124]

Benton, M.D., and Ann Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 ("Spitz Article") ")[FDA FOIA Release: MIF 006692-97]. The members of the FDA Advisory Committee who were still working for FDA at the time of publication received a copy of the Spitz Article. *See* Medical Officer's Review, *infra* Appendix A, at 29. Although FDA considered data from the entire U.S. Clinical Trial, it appears that the agency formally approved Mifeprex based only on the portion of the U.S. Clinical Trial data that was generated among women whose pregnancies were no more than 49 days' gestational age. *See* Mifeprex Approval Memo, *infra* Appendix A, at 1 ("The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period."). *See also* Mifeprex Label ("Clinical Studies").

[118] Among the inclusion criteria were requirements that a patient be at least 18 years old, be in good health, have an intrauterine pregnancy of no more than 63 days (confirmed by a pelvic examination *and* ultrasound), and have agreed to a surgical abortion if the mifepristone-misoprostol abortion failed. Medical Officer's Review, *infra* Appendix A, at 7-8. The study excluded women with certain health problems, such as liver, respiratory, or renal disease, cardiovascular disease, chronic hypertension, anemia, clotting problems, pelvic inflammatory disease, and ectopic pregnancies. *See id.* at 8. In addition, women who were over 35 and smoked, had IUDs, were breastfeeding, were unlikely to comply with study requirements, or who "[l]ived or worked more than one hour from the emergency care facility" were excluded. *See id.* at 8-9.

[119] *See* Medical Officer's Review, *infra* Appendix A, at 8.

[120] Medical Officer's Review, *infra* Appendix A, at 9.

[121] *See* Medical Officer's Review, *infra* Appendix A, at 9.

[122] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[123] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[124] Medical Officer's Review, *infra* Appendix A, at 16.

The U.S. Clinical Trial consisted of 2,121 subjects.[125] Of these patients, 2,015 were evaluated for efficacy,[126] which "was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[127] The remaining 106 patients did not return for the third visit.[128] The mifepristone-misoprostol combination was effective in 92 percent of patients with pregnancies no greater than 49 days, 83 percent of patients with pregnancies between 50 and 56 days, and 77 percent of women with pregnancies between 57 and 63 days.[129] All 2,121 subjects were evaluated for safety.[130] Ninety-nine percent of patients experienced adverse events and most of these experienced multiple adverse events.[131] Twenty-three percent of the adverse effects experienced by each gestational age group were "severe."[132]

Finally, FDA did not conduct a statistical review of the results of the U.S. Clinical Trial. FDA's statistical reviewer explained this failure by noting that "[a] statistical evaluation of the European studies was completed previously "and "[t]he clinical results of the supporting U.S.

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[125] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[126] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[127] Medical Officer's Review, *infra* Appendix A, at 16. The failure to establish a pre-trial, statistical definition for drug efficacy was a defect in trial design.

[128] *See* Medical Officer's Review, *infra* Appendix A, at 16. It would have been appropriate to include these 106 patients in the efficacy analysis as "failures," if for no other reason than that they did not appear for all three required visits. Although "[f]or 92 of these patients, there was some information suggesting a successful outcome," *id.* at 10, there was neither definitive evidence of complete abortion nor, apparently, any information with respect to whether these women subsequently experienced any adverse effects. In fact, during their second visit, five of these 106 women were diagnosed as having continuing pregnancies. *Id.* at 10. *See also* Spitz Article, *infra* Appendix A, at 1246 ("The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women.").

[129] *See* Medical Officer's Review, *infra* Appendix A, at 11 (Table 1).

[130] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[131] *See* Medical Officer's Review, *infra* Appendix A, at 11.

[132] *See* Medical Officer's Review, *infra* Appendix A, at 11.

studies . . . are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required."[133]

2. Requirements for Proving Drug Safety and Effectiveness

FDA has developed a rigorous default standard for scientific demonstrations of safety and effectiveness of human drug products.[134] Section 505(d)(5) of the FD & C Act provides, in relevant part, that FDA shall refuse to approve a new drug application 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."[135] Section 505(d) defines "substantial evidence" to mean "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 . . . ."[136] FDA has stated that "substantial evidence" requires a showing of clinically significant evidence of effectiveness rather than mere statistical evidence of significance.[137] No such showing was made for Mifeprex, which has been demonstrated to be less effective than surgical abortion for all segments of the population.

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[133] FDA, "Statistical Comments on Amendment 024," Memorandum to File NDA 20-687 (Feb. 14, 2000). This document is available along with the agency's Statistical Review. *See* Statistical Review, *infra* Appendix A.

[134] *See* the discussion of the development and requirements of FDA's "gold standard," *supra* Section III.C.1.

[135] 21 U.S.C. § 355(d)(5).

[136] 21 U.S.C. § 355(d) ("the term '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, on the basis of which it could fairly and responsibly be concluded by such experts 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 labeling or proposed labeling thereof.").

[137] *See Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 155 (D.C. Cir. 1986) ("It is important to note that the Commissioner does not contend that the effectiveness shown must amount to a 'medical breakthrough', as ARW complains, but contends in his brief that he would be satisfied with even a modest clinical or therapeutic effect.").

Section 314.126 of FDA's rules states that "[r]eports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."[138] The rule states that a major purpose of an adequate and well-designed study is to "permit[ ] a valid comparison with a control to provide a quantitative assessment of drug effect."[139] According to Section 314.126(b), an adequate and well-controlled study serves to ensure that the subjects of the trial have the disease or condition being studied,[140] that the method of assigning patients to treatment and control groups minimizes bias (*e.g.*, using randomization),[141] and, that "[a]dequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data" (*e.g.*, blinding).[142] The criteria that the rule establishes "have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation."[143]

Agency guidance provides that FDA may approve an NDA based on only one, not two, effectiveness trials for drugs in one of the following three categories:

> 1) when effectiveness may be demonstrated adequately with existing studies of another claim or dose (e.g., approval for pediatric use on the basis of studies in adults); 2) when a controlled trial of a specific new use is supported by evidence from adequately controlled trials from related uses, dosages, or endpoints; and 3) when a single multicenter trial provides statistically convincing and clinically meaningful evidence of effectiveness, supported by confirmatory research.[144]

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[138] 21 C.F.R. § 314.126(a) ("Adequate and well-controlled studies.").

[139] 21 C.F.R. § 314.126(b)(2) (describing "placebo concurrent control," "dose-comparison concurrent control," "no treatment concurrent control," "active treatment concurrent control," and "historical control").

[140] 21 C.F.R. § 314.126(b)(3).

[141] 21 C.F.R. § 314.126(b)(4).

[142] 21 C.F.R. § 314.126(b)(5).

[143] 21 C.F.R. § 314.126(a).

[144] Kulynych, *infra* Appendix A, at 146 (citing FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) at 5-17 (*FDA Effectiveness Guidance*).

Mifepristone did not fall within any of these categories. The first and second categories were inapposite because mifepristone had not been approved for any use in any population in the United States; additionally, no evidence from adequate and well-controlled trials had ever been presented to FDA regarding any use for mifepristone. Because neither the French Clinical Trials nor the U.S. Clinical Trial was randomized, blinded,[145] or comparator-controlled, none of these trials could provide the type of data necessary for the third category either. Furthermore, these studies lacked "clear, prospectively determined clinical and statistical analytic criteria."[146]

Even though FDA takes the position elsewhere that the extent to which a trial's design controls for various types of bias "is a critical determinant of its quality and persuasiveness,"[147] neither the French Clinical Trials nor the U.S. Clinical Trial were randomized, concurrently controlled, or blinded. A control group "allow[s for] discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment."[148] Control groups also enable investigators to

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[145] Blinding is the normal method by which those who evaluate a medication's effectiveness and side effects, are kept unaware of whether they are evaluating the comparator drug (sometimes a placebo), or the new medication (or procedure) under study. If possible, the patient is also blinded and not allowed to know which treatment she is receiving ("double-blinding"). According to standard scientific and medical practice and the standards to which FDA holds pharmaceutical sponsors, all clinical research studies investigating the effects of new drugs should be subjected to an assessment by a blinded evaluator. Conducting a concurrently-controlled, randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable. There are study designs that would have also allowed for blinding. Had blinding proved too difficult to perform, the requirement could have been waived based upon a satisfactory showing by the sponsor.

[146] *FDA Effectiveness Guidance*, *infra* Appendix A, at 12.

[147] FDA, "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials," (Rockville, Md.: May 2001) at 3 (§ 1.2.1) (*FDA Guidance (ICH: E10): Choice of Control Group*). FDA's publication of "E10" is available at: <http://www.fda.gov/cder/guidance/4155fnl.pdf>.

[148] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2) (Introduction, "Purpose of Control Group").

determine "what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective."[149]

A trial that employs a concurrent control group drawn from the same population yields the most robust data. Concurrent control groups are chosen from the same population as the test group and are "treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time."[150] When concurrent control groups are used, the treatment and non-treatment groups are similar in all baseline and non-treatment variables that could influence the outcome or introduce bias into the study.[151]

By contrast, in a trial using external or historical controls "the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group."[152] FDA cautions:

> "The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome). Use of the latter comparator is particularly treacherous (such trials are usually considered uncontrolled) because general impressions are so often inaccurate."[153]

In such a trial, "[t]he control group is thus not derived from exactly the same population as the treated population."[154] If, as is most common, the external control group is composed of "a well-documented population of patients observed at an earlier time," the trial is said to be

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[149] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[150] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[151] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2). "Bias here . . . means the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value." *Id.*

[152] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

[153] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 5 (§ 1.3.5).

[154] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

"historically" controlled.[155] Blinding and randomization are also not available to minimize bias when external or historical controls are used.[156]

According to FDA, the "[i]nability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable."[157] A legal commentator recently cautioned courts about the scientific validity of experiments and trials that have no concurrent control.[158] She explained that "historically controlled subjects have not been subjected to exactly the same conditions as the test subjects."[159] Consequently, "one must be wary of" non-concurrently controlled studies (*i.e.*, historical, external, or uncontrolled studies) because their conclusions can be manipulated more easily than if concurrent controls are used.[160]

3. FDA's Acceptance of the French and U.S. Clinical Trial Data Violated Section 314.126(e) of the Agency's Rules

Section 314.126(e) of FDA's rules states unequivocally that "[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness."[161] The section authorizes the use of uncontrolled trials merely to present supporting evidence for controlled trials; uncontrolled trials, if they are "carefully conducted and

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[155] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1) ("but it could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study.").

[156] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.2).

[157] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.2).

[158] Erica Beecher-Monas, "The Heuristics of Intellectual Due Process: A Primer for Triers of Science," *New York University Law Review* 75: 1563-1657, 1628.

[159] Beecher-Monas, *infra* Appendix A, at 1628, n.357.

[160] Beecher-Monas, *infra* Appendix A, at 1628, n.357 (" 'you can prove anything with selective controls,' so one must be wary of historical controls," Beecher-Monas quoting Jon Cohen, "Cancer Vaccines Get a Shot in the Arm," 262 Science 841, 843 (1993)).

[161] 21 C.F.R. § 314.126(e)(emphasis added).

documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug."[162]

FDA recognizes a limited role for external, historically controlled studies. The agency takes the position that "[h]istorical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference."[163] Similarly, Section 314.126 cautions that "[b]ecause historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent controlled populations, historical control designs are usually reserved for special circumstances."[164] FDA cites as an example, "studies of diseases with high and predictable mortality (for example, certain malignancies),"[165] in which a decision might be made to offer all trial participants a potentially effective drug. Externally controlled studies also may suffice because "the effect of the drug is self-evident (general anesthetics, drug metabolism)."[166]

The French and U.S. Clinical Trials, which did not employ either external or historical control groups, were uncontrolled. During the Advisory Committee Hearings, FDA's Dr. Ridgley C. Bennett, who summarized the data from the French Clinical Trials, stated:

> There are very few studies comparing medical methods and vacuum aspiration for termination of early pregnancy. To date, no large randomized controlled trials have compared mifepristone plus misoprostol with suction curettage abortion. However, large published series have demonstrated morbidity rates associated with mifepristone plus prostaglandin to be similar to those of suction-curettage.[167]

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[162] 21 C.F.R. § 314.126(e).

[163] *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.2.2.2). According to FDA guidance, the "main advantage" of an externally controlled trial "is that all patients can receive a promising drug, making the study more attractive to patients and physicians." *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.6).

[164] 21 C.F.R. § 314.126(b)(2)(v) ("Historical control.").

[165] 21 C.F.R. § 314.126(b)(2)(v).

[166] 21 C.F.R. § 314.126(b)(2)(v).

[167] FDA Hearings Transcript, *infra* Appendix A, at 130. Jensen and his fellow researchers conducted "[a] prospective, noncurrent, single center cohort comparison." See Jensen Study, *infra* Appendix A, at 153. The study

"Published series" and uncontrolled studies cannot serve as a substitute for the well-controlled clinical trials that FDA requires. A concurrent control group would have been feasible because the trial participants were prepared to receive surgical abortion in the event of a failed mifepristone abortion.

The unusual circumstances that sometimes justify relying on externally controlled trials are not applicable with respect to pregnancy termination, generally, or the termination using mifepristone and misoprostol, specifically. Randomized, concurrently-controlled, blinded trials would have allowed investigators to compare not only the relative rates of complete termination and expulsion, but also the nature, intensity, and duration of the numerous side effects. In the absence of concurrent controls and blinding, the duration and intensity of cramping, nausea, bleeding, pain, and any emotional or psychological effects of the treatments would be subject to investigator and patient bias. The design of the U.S. Clinical Trial precluded unbiased comparison groups that could have helped analysts arrive "at a complete understanding of potential advantages, disadvantages and differences" between medical and surgical abortion.[168] FDA's *de facto* waiver of Section 314.126(e) constituted a gross departure from its past practice and announced standards for the conduct of adequate and well-controlled clinical trials.[169]

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compared the data from Mifeprex patients at one of the sites that participated in the U.S. Clinical Trial with data from patients who subsequently underwent surgical abortions at the same site. Although the methodological quality of this study is arguably superior to either the French or U.S. Clinical Trials, had it been offered as trial data it also would have been a weak substitute for a randomized controlled trial establishing equivalent or superior efficacy to surgical abortion.

[168] *See* Jensen Study, *infra* Appendix A, at 156. Dr. Cassandra Henderson, a member of the FDA Advisory Committee, wondered about this point as well: "Since this regimen is not without any side effects and we know that spontaneous abortion is not an infrequent occurrence, is it appropriate to use historical controls in trying to evaluate the efficacy of this regimen and not a randomized placebo trial?" FDA Hearings Transcript, *infra* Appendix A, at 131 (FDA's Dr. Ridgely C. Bennett gave the following puzzling response: "Well, I think it would be difficult to do a randomized trial of this nature. But I think it is fair to use a historical control for efficacy.").

[169] There is no evidence that FDA formally issued a waiver under Section 314.126(c) of the requirement for well-controlled studies or that the Population Council ever requested such a waiver.

4. Subpart H's Standard for Proving Drug Effectiveness

The approval of a drug under Subpart H does not lower the applicable standards for proving the drug's effectiveness. As FDA stated when it adopted Subpart H, "[a]ll drugs approved [under Subpart H] will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."[170] In fact, Subpart H is available only for drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients *over existing treatments* (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."[171] Neither the French nor the U.S. Clinical Trials yielded scientifically valid comparisons with the existing therapy, surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments." FDA should have required the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone has a meaningful therapeutic benefit over the standard method for terminating pregnancies. FDA did not require the drug sponsor to perform such trials for Mifeprex, which departs from FDA's normal treatment of Subpart H drugs generally and for the other drugs approved under the restricted distribution provisions in Section 314.520.

Mifeprex appears to be the only drug that FDA has approved under Section 314.520 of Subpart H without requiring compliance with the statutory and regulatory requirements that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials capable of providing data for subjection to rigorous statistical analysis.

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[170] *Subpart H Final Rule*, 57 Fed. Reg. at 58953.

[171] 21 C.F.R. § 314.500 (emphasis added). The class of "existing treatments" to which there must be a comparison, as specified in this rule section, is not limited to pharmaceuticals. For example, a potential chemotherapeutic agent might be compared to radiation therapy.

Aside from Mifeprex, only four drugs have been approved pursuant to Section 314.520, the restricted distribution prong of Subpart H. Each of these drugs, Xeloda,[172] Thalomid,[173] Actiq,[174] and Tracleer,[175] was an appropriate candidate for approval under Section 314.520. Moreover, in each case, studies were performed that allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care. FDA's decision to require randomized, comparator-controlled, blinded trial design for each drug, even in the face of urgent need for the treatments at issue, supports the claim that FDA's treatment of the mifepristone NDA was aberrant.

Xeloda™ (capecitabine) was approved for use in treating patients with widely metastatic ("Stage IV") terminal breast cancer, for whom all other modalities of chemotherapy have failed or are contraindicated.[176] The average lifespan of a patient with multi-drug resistant tumors participating in the clinical trials for this drug was only 8.5 months. Because Xeloda was only modestly effective (25% of the recipients improved for an average of five months), exhibited significant toxicity, and was a last resort treatment for dying patients, FDA approved it under Section 314.520 with use restrictions and commitments to further study the drug. Subsequent randomized, concurrent controlled, blinded evaluator trials demonstrated Xeloda's statistical superiority to the standard of care for metastatic colon and breast cancers.[177]

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[172] NDA 20896.

[173] NDA 20785.

[174] NDA 20747.

[175] NDA 21290.

[176] *See* "NDAs Approved under Subpart H," *infra* Appendix A. The current version of the Subpart H approval chart (updated Aug. 8, 2002) indicates that Xeloda is a "surrogate endpoint" drug, rather than a restricted distribution drug. However, the two previous postings of the chart state the opposite. Furthermore, FDA's approval letter states that the NDA "[was] approved under 21 CFR 314.520." Letter, FDA/CDER to Cynthia Dinella, Group Director, Regulatory Affairs, Hoffman-La Roche Inc. (Apr. 30, 1998).

[177] *See* Xeloda package insert.

Thalidomide (Thalomid™) was approved under Section 314.520 for the treatment of leprosy, a disfiguring, chronically disabling, and often lethal skin infection.[178] Thalidomide is a drug the severe toxicity of which, particularly to fetuses, is well-documented. Children exposed to this drug *in utero* suffer dramatic birth defects, namely the partial absence of hands, feet, arms and legs. The public outcry following the discovery that thalidomide causes these alarming malformations helped to spur the scientific modernization of FDA drug approval policy and practices in the 1960s. Clinical trials involving leprosy are difficult and require long periods of time because the disease is very rare in the United States. Three randomized, double-blinded comparator-controlled clinical trials were performed to support the Thalomid NDA.[179]

Oral fentanyl citrate (Actiq™) was approved under Section 314.520 as a powerful sedating narcotic painkiller, primarily for use to relieve the suffering of dying cancer patients.[180] Actiq can be lethal, particularly to children, because it quickly abolishes a patient's drive to breathe, unless the patient is already accustomed to narcotic analgesics. Moreover, Actiq, a powerful narcotic, has a high potential for abuse and diversion into the illegal drug market. Actiq was evaluated in a "double blinded, placebo controlled" study for the treatment of breakthrough cancer pain and was shown to "produce statistically significantly more pain relief compared with placebo."[181] Actiq is restricted for use only by oncologists and pain specialists who are familiar with the management of the side effects and complications of the drug's use as approved.

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[178] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[179] *See* Thalomid package insert.

[180] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[181] Actiq package insert.

Tracleer™ (bosentan tablets) was approved pursuant to Section 314.520 for use in treating pulmonary hypertension, a life threatening and frequently progressive condition of excessively high blood pressure in the lung blood vessels resulting from chronic scarring and injury of the lung tissue.[182] Tracleer can cause liver damage and major birth defects. Two randomized, double-blinded, placebo-controlled clinical trials demonstrated the superiority of the drug over a placebo. Tracleer was compared to a placebo because there is no alternate standard of care for pulmonary hypertension. Despite its potential toxicity, Tracleer was approved subject to usage restrictions under Section 314.520 because it is the only treatment available for a life threatening and debilitating condition.[183]

5. FDA Failed to Require a Comprehensive Audit of French Clinical Trial Data after Discovering Violations of Good Clinical Practices

In June 1996, FDA inspected the trial records of a "French government-supported abortion clinic" that participated in the French Clinical Trials. FDA issued a Form 483 detailing problems uncovered during the inspection. The problems identified by the investigator suggested carelessness, fraud, evidence tampering, and the systematic under-reporting of serious adverse events. The inspection "revealed a failure to maintain complete and accurate records." The violations that were discovered included: "laboratory reports that were missing" for 11 patients, "missing ultrasound documents" for 20 patients, "pages missing from the case record files and unreported aspirations," inclusion of 4 ineligible patients, and "consent forms were dated after the start of study for some subjects, and the investigator had signed consent form

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[182] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[183] *See* Tracleer package insert.

sometimes in advance, up to 4 days before the subjects had signed."[184] There were also "under-reported side effects" such as "a patient bleeding with two subsequent aspirations; convulsions reported as fainting; and expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain."[185] After elaborating on the deficiencies found, the FDA inspector concluded: "Notwithstanding these objectionable conditions, [redacted name of an FDA official] assured Dr. Aubeny that he would not recommend that the studies not be included in the evaluation of the NDA application."[186]

FDA should not have allowed tainted data to support the Mifeprex NDA. A complete audit of all French Clinical Trial data is warranted to determine whether another set of clinical trials must be performed to replace the tainted French trial data.

F. THE AGENCY'S DE FACTO APPROVAL OF MISOPROSTOL'S NEW USE WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

When FDA approved Mifeprex, it also took action with respect to a second drug – misoprostol. Taken alone, mifepristone is ineffective as an abortifacient.[187] In order to achieve an abortion rate greater than 90 percent, the administration of mifepristone is followed approximately two days later by a prostaglandin to complete the abortion. In the U.S. Clinical

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[184] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1 [FDA FOIA Release: MIF 004135-45].

[185] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1.

[186] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 9.

[187] Although some studies using mifepristone alone have produced completion rates as high as 60 to 80 percent, it is widely recognized that, on its own, mifepristone is not a viable substitute for surgical abortion. *See, e.g.,* Mitchell D. Creinin, "Early Medical Abortion with Mifepristone or Methotrexate: Overview," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 3 (reporting that "[f]or gestations up to 49 days, complete abortion occurs in approximately 60% to 80%" of women using mifepristone alone); Helena von Hertzen, M.D., "Research on Regimens for Early Medical Abortion," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 133-36.

Trial, the prostaglandin used was misoprostol, which was distributed by G.D Searle & Co. ("Searle") as the anti-ulcer drug Cytotec™.[188] Ultimately, FDA based its approval of Mifeprex on the combined action of a mifepristone and misoprostol regimen. On the day FDA approved mifepristone, it notified Searle that "[t]he drug mifepristone is now approved in a regimen with misoprostol for termination of pregnancy of 49 days or less."[189]

Searle, which opposed the use of its drug in conjunction with Mifeprex as an abortifacient,[190] did not file a Supplemental NDA for the use of misoprostol as part of an abortion regimen.[191] Absent such an application, FDA lacked the basis for sanctioning a new indication for misoprostol. As Peter Barton Hutt, former FDA general counsel, observed, the agency's treatment of misoprostol "set[ ] an extraordinary precedent" because FDA was "seemingly

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[188] After a series of corporate transactions, Searle is now part of Pharmacia Corporation, which is headquartered in Peapack, New Jersey. In 1985, G.D. Searle & Co. became the pharmaceutical unit of Monsanto. In April 2000, Monsanto merged with Pharmacia & Upjohn to create the Pharmacia Corporation. Pharmacia & Upjohn had been created in 1995 when Pharmacia AB and the Upjohn Company merged. On July 15, 2002, Pfizer Inc. announced that it would purchase Pharmacia.

[189] Letter, Dr. Lilia Talarico, M.D., Director, FDA/CDER, Division of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III to Dr. Mary Jo Pritza, G.D. Searle & Co. (Sept. 28, 2000): at 1 [FDA FOIA Release: MIF 008847-48]. The Talarico Letter came in response to the August 8, 2000 application by Searle to obtain approval for changes that would have bolstered the Cytotec label's discussion of adverse effects (presumably in anticipation of FDA's approval of the mifepristone NDA). FDA chided Searle for attempting to make the proposed changes and summarily rejected them. *Id.* at 1. When it announced the Mifeprex approval, FDA referred to the "approved treatment regimen." *See* FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000). *See also* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 4 (referring to the "mifepristone treatment regimen").

[190] In fact, on August 23, 2000, Searle wrote an open letter to all health care practitioners stating that "Cytotec is not approved for the induction of labor or abortion." The letter listed a number of potential "[s]erious adverse events reported following off-label use of Cytotec in pregnant women includ[ing] maternal or fetal death." Michael Cullen, M.D., Medical Director U.S., Searle, Open Letter to Health Care Providers (Aug. 23, 2000)[FDA FOIA Release: MIF 008022]. Officials of the American College of Obstetricians and Gynecologists, among others, decried Searle's lack of cooperation. *See* Ralph W. Hale, M.D., and Stanley Zinberg, M.D., "The Use of Misoprostol in Pregnancy," editorial, *New England Journal of Medicine* 344 (Jan. 4, 2001): 59-60. FDA's approval of the Mifeprex Regimen in the face of Searle's opposition appears to have usurped Searle's rights to control the distribution of its drug.

[191] Because Searle's patent on misoprostol did not expire until July 2000, no other party would have been able to file a timely supplemental NDA for the use of a generic form of misoprostol as an abortifacient.

encouraging a drug's unapproved use."[192] He added that the agency is in an "embarrassing and uncomfortable position."[193] FDA did more than encourage the unapproved use of misoprostol; it *mandated* the unapproved use.

1. Misoprostol's Use as an Abortifacient is a New Indication for which the Requisite Supplemental New Drug Application Was Not Filed

A drug that differs in any material way (including in composition, effect, or intended use) from an approved drug is a new drug that must independently be established to be safe and effective.[194] Furthermore, a drug already being used to treat one disease or part of the body may be a new drug when used to treat another disease or part of the body.[195] Misoprostol's new use as an abortifacient, therefore, marks it as a "new drug."[196]

New drugs must be shown to be safe and effective. Specifically, FDA requires that "[a]ll indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) . . . unless the requirement is waived . . . ."[197]

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

[193] Zimmerman at B1.

[194] *See Thompson v. Western Medical Center*, Brief for the Petitioners (filed by the Solicitor General of the United States), No. 01-344 (Dec. 2001): at 4 ("See *United States v. Generix Drug Corp.*, 460 U.S. 453, 460-461 (1983) (determination whether a product is a new drug takes into account both active and inactive ingredients); 21 C.F.R. 310.3(h) (discussing factors that make a drug a 'new drug').

[195] A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

[196] The "newness" of misoprostol in this indication was heightened by the fact that, when Mifeprex was approved, misoprostol was explicitly contraindicated for pregnant women. The misoprostol label included the following black-box warning: "CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT . . . ." In April 2002, the Cytotec label was changed to "remove[ ] the contraindication and precaution that Cytotec should not be used in women who are pregnant." FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). The label now restricts the contraindication to pregnant women who are using Cytotec as a non-steroidal anti-inflammatory drug ("NSAID"). The revised Cytotec label and, more specifically, the "Indications and Usage" section, however, continue to lack any reference to the use of misoprostol in the Mifeprex Regimen.

[197] 21 C.F.R. § 201.57(c)(2). To the best of the Petitioners' knowledge, FDA did not formally waive the requirement for misoprostol as part of an abortion regimen.

A Supplemental NDA provides the necessary evidence in support of a new indication.[198] Absent a waiver, a Supplemental NDA permits FDA to consider the evidence in support of the proposed change and approve related labeling changes in advance.[199] Even though a new use for misoprostol is an integral part of the Mifeprex Regimen, FDA sanctioned this new misoprostol indication without having received and considered a Supplemental NDA.

Among the changes for which FDA approval is necessary are changes to statements in a drug's labeling indicating whether "[t]he drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy."[200] A well-known treatment regimen illustrates how FDA has typically dealt with the labeling of two drugs that have been approved for combined use. The regimen pairs methotrexate and Leucovorin Rescue. Methotrexate, a chemotherapeutic agent, kills cancer cells by depriving them of folic acid which is necessary for DNA synthesis, but, in the process, methotrexate deprives normal bone marrow cells of the folic acid they need. Leucovorin Rescue serves as an antidote to the toxic effects of methotrexate. The labeling for Leucovorin Rescue refers to its use "after high-dose methotrexate therapy in osteosarcoma," which is an approved

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[198] A recent article noted: "To obtain FDA approval for an additional use of a previously approved drug, the sponsor must submit a supplemental application (sNDA, sBLA, or sPMA) demonstrating the safety and efficacy of the drug when used in the new way or for the new indication. The supplemental application typically requires clinical data similar to those in the original application, but does not require the same extensive chemistry, manufacturing and controls, and preclinical pharmacology and toxicology data as in the original application." Shane M. Ward, "*Washington Legal Foundation* and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet," *Food and Drug Law Journal* 56 (2001): 41-56, at 44 (citations omitted).

[199] *See* 21 C.F.R. § 314.70(b). *See also* Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1775 ("FDA takes the position, which no manufacturer has sought to challenge in court, that any potentially significant modification of an approved new drug [application] likewise requires advance agency approval. As a consequence, not only attempts to expand the indications for a drug but other changes in labeling, in inactive ingredients, in the method or location of manufacture, or in packaging must first be the subject of an approved Supplemental New Drug Application.").

[200] *See* 21 C.F.R. § 201.57(c)(1)(iv).

indication for methotrexate.[201] Similarly, methotrexate's labeling refers to an approved use of Leucovorin Rescue.[202]

By contrast, in the Mifeprex labeling, an *unapproved* indication for misoprostol is discussed. In approving such labeling, FDA has taken the aberrant position that the maker of one drug (Mifeprex) can secure approval of a new indication for another company's drug (misoprostol) merely by describing that new use as part of a combined therapy. FDA circumvented its own regulations by failing to require that both drugs in the Mifeprex Regimen be approved for the indication in question – pregnancy termination.[203]

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[201] *See* Leucovorin Calcium for Injection Package Insert ("Indications and Usage") ("Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists."). The package insert is available at: <http://www.xanodyne.com/leucovorin_calcium_pl_2002.pdf>.

[202] The methotrexate package insert states that "[m]ethotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor." The package insert is available at: <http://www.rxlist.com/cgi/generic/mtx_ids.htm>.

[203] A recent approval of a biologic product also illustrates the principle that FDA-approved labeling lists only approved indications. On February 19, 2002, FDA approved Zevalin for use in combination with Rituxan (rituximab) to treat low-grade B-cell non-Hodgkins Lymphoma (NHL). Rituxan had been approved previously and was already indicated "for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma." *See* Rituxan Package Insert ("Indications and Usage"). Rituxan and Zevalin are monoclonal antibodies that can significantly shrink tumors by targeting white blood cells (B-cells) including malignant B cells. The "Indications and Usage" section of Zevalin's label describes the drug as being "part of the ZEVALIN therapeutic regimen (see Dosage and Administration)." The "Dosage" section directs that Rituxan be administered and then followed by Zevalin on Day One and then again seven to nine days later. After the Zevalin NDA was approved, detailed information about the administration of the "Zevalin Therapeutic Regimen" was added to the Rituxan label. On February 19, 2002, FDA's Center for Biologics Evaluation and Research approved a supplement to the Rituximab biologics license application "to revise the dosage and administration section of the package insert to include information regarding the use of Rituximab as a component of the Zevalin therapeutic regimen . . . ." Letter, Dr. Karen D. Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, to Alice Wei, IDEC Pharmaceuticals (Feb. 19, 2002) (*see* <http://www.fda.gov/cber/approvltr/rituide021902L.htm>).

2. FDA Sanctioned the Promotion of Misoprostol for an Unapproved Use as Part of the Mifeprex Regimen

The use of misoprostol as an abortifacient is an unapproved or "off-label" use.[204] FDA objects to the *promotion* of off-label uses of drugs by manufacturers.[205] "Off-label" uses of drugs are common as physicians explore new ways of using approved drugs, but normally FDA strives to ensure that physicians and patients are not misled into believing that FDA has approved such uses. In an effort to curb the promotion of off-label uses by pharmaceutical manufacturers, FDA issued regulatory guidance in 1996 pertaining to the dissemination of off-label use information.[206] In this case, however, FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol. FDA oversaw the creation of the promotional materials for Mifeprex,[207] which discussed the off-label use of misoprostol.[208] FDA itself disseminated information about

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[204] *See generally* James M. Beck and Elizabeth D. Azari, "FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions," *Food & Drug Law Journal* 53 (1998): 71-104, at 71 n.2, which explains "off-label" use as follows:

> "Off-label" has more accurately been termed "extra label" use. It means only that a product is used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely. *See, e.g., Washington Legal Found. v. Kessler*, 880 F.Supp. 26, 28 n.1 (D.D.C. 1995). . . . Off-label can mean many things. "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use." William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (footnotes omitted).

[205] *See, e.g., Subpart H Final Rule*, 57 Fed. Reg. at 58,953 ("Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved.").

[206] *See* FDA, "Advertising and Promotion; Guidances," Notice, 61 Fed. Reg. 52,800 (Oct. 8, 1996) (publishing two guidance documents: "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data" and "Guidance for Industry Funded Dissemination of Reference Texts").

[207] FDA reminded the Population Council in the Mifeprex Approval Letter that, pursuant to 21 C.F.R. § 314.550, the drug sponsor is obligated to submit Mifeprex promotional material for review by the agency prior to dissemination to physicians and the public. *See* Mifeprex Approval Letter at 3.

[208] A Danco Laboratories webpage, for example, contains the following question and answer:

> Q: How Does Mifeprex Work?
>
> A: Mifeprex blocks progesterone, a hormone necessary for a pregnancy to continue. You take Mifeprex followed by a prostaglandin, misoprostol, which causes uterine contractions that help to end pregnancy.
>
> In more detail, Mifeprex blocks progesterone, a naturally produced hormone that prepares the lining of the uterus for a fertilized egg and helps maintain pregnancy. Without progesterone, the lining of the uterus

the off-label use of misoprostol in documents such as the press release announcing the approval of Mifeprex for use in conjunction with misoprostol.[209] Recently it did so again when the agency emphasized the importance of adhering to the approved regimen, including the off-label use of misoprostol.[210]

3. Mifeprex Is Misbranded: Its Labeling Promotes an Unapproved Use of Another Drug

The labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved.[211] FDA's ability to regulate the marketing and distribution of drugs rests largely on its legal capacity to strictly control the content of a drug's labeling. A fundamental tenet of drug regulation is that FDA requires approval for every indication listed in the labeling of a drug.[212] FDA would undercut its own authority if it did not also apply this rule to uses for a drug referenced on another drug's labeling.

The Mifeprex labeling creates false expectations about misoprostol. Physicians and patients are justified in believing that any use or indication for a drug, included in the "Indication

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softens, breaks down and bleeding begins. Mifeprex is followed by a prostaglandin that causes the uterus to contract, which helps to complete the process. . . . The prostaglandin used following Mifeprex is misoprostol, a drug already available in the United States.

"Using Mifeprex: Frequently Asked User Questions," Danco Laboratories website at <http://www.earlyoptionpill.com/may_faqs.php3>. The electronic version of the Mifeprex Label contains a hyperlink to the Danco Laboratories website, <www.earlyoptionpill.com>, which contains the above-referenced webpage. (When printed, the hyperlink appears to be ordinary text.)

[209] *See*, FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000) ("Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin.").

[210] *See* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 6. In this same document, however, FDA cautions health care providers against "using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses . . . ." *Id.* at Question 9.

[211] Misoprostol receives more than a passing mention on the Mifeprex Label; the word "misoprostol" appears 34 times (compared to 57 appearances of "mifepristone" and 34 appearances of "Mifeprex").

and Usage" section of an FDA-approved label, has been subjected to the rigorous approval process set forth in Section 505 of the FD&C Act. Section 201.6(a) of the Agency's rules states that misbranding may arise from "a false or misleading representation with respect to another drug."[213] "When a physician, manufacturer, or *other third party* steps in to promote an unapproved use of a drug by advertising or distribution to other physicians, the drug may become unlawful under Section 301(k) the FD&C Act, 21 U.S.C. § 331(k)(1994), which prohibits misbranding, and Section 502(f)(1), 21 U.S.C. § 352(f)(1)(1994), which requires a drug's labeling to bear 'adequate directions for use.'"[214] Mifeprex is, therefore, misbranded.

Mifeprex is also misbranded because it is unsafe when used as directed in the approved labeling. Section 502(j) of the FD& C Act states that "[a] drug or device shall be deemed to be misbranded . . . [i]f it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."[215] As discussed in the next section, FDA's approved regimen is unsafe because it lacks important safeguards.

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[212] *See* Elizabeth A. Weeks, "Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 645-65, at 647 n.13 (citing Merrill, (*infra* Appendix A), at 1853).

[213] *See* 21 C.F.R. § 201.6(a).

[214] Merrill, *infra* Appendix A, at n.318 (emphasis added). *See also* 21 C.F.R. § 314.530(a)(5) (authorizing the Secretary to withdraw approval of a Subpart H drug if "[t]he promotional materials are false or misleading").

[215] 21 U.S.C. § 352(j). *See also* Jeffrey N. Gibbs and Judith E. Beach, "Chapter 7: Adulteration and Misbranding of Drugs" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 229 ("When the drug is dangerous to the health of the user even when used as recommended on the label, it is misbranded.").

G. WOMEN'S LIVES ARE BEING ENDANGERED BY THE LACK OF SAFEGUARDS IN FDA'S APPROVED REGIMEN

On February 18, 2000, FDA informed the Population Council that "adequate information ha[d] *not* been presented to demonstrate that [mifepristone], when marketed in accordance with the terms of distribution proposed [by the Population Council], is safe and effective for use as recommended."[216] Over the next several months, the Population Council and Danco refused to supplement its distribution plan with a meaningful patient safety component. This prompted FDA, on June 1, 2000, to privately convey to the sponsor a set of proposed restrictions intended to rectify the sponsor's omission. The agency's proposed restrictions were soon leaked to the public. Amidst a vigorous political and editorial backlash, the sponsor not only rejected FDA's proposal but, in what was described by FDA as a "very significant change," repudiated restrictions the sponsor itself had proposed in 1996.[217] FDA succumbed and soon approved a regimen that did not embody restrictions sufficient to address the agency's legitimate safety concerns.

Early in the approval process, FDA expressed its intention to place restrictions on the use of mifepristone.[218] FDA's position was informed, in part, by the international experience with

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[216] 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5 (emphasis added).

[217] *See* FDA Email (June 23, 2000): at 1 (explaining that the Population Council's attorney "affirmed that the 1996 proposals for distribution system as presented by the Pop Council then and agreed to by the [FDA Advisory Committee] and FDA are NOT what the Pop Council wants today. I explained that this change is very significant and that they need to provide their justification/rationale.")[FDA FOIA Release: MIF 002523].

[218] In order to allay concerns of the drug's European owner, FDA pledged, in the course of securing the U.S. patent rights for the Population Council, to "take appropriate measures . . . to assist through the NDA-approval process in the creation of a regime for the distribution and use that will protect against misuse of the drug." Letter, David A. Kessler, Commissioner of Food and Drugs, to the President & CEO of Roussel Uclaf [name redacted] and to Margaret Catley-Carlson, President of Population Council (May 16, 1994): at 1 [FDA FOIA Release: MIF 004992-93].

mifepristone.[219] The NDA submitted by the Population Council on March 14, 1996 included a plan that would have limited distribution of mifepristone to "licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted]), who will attend educational seminars on the safe use of this regimen."[220]

The FDA Advisory Committee, when it met in July 1996, was not satisfied with the restrictions proposed by the Population Council and expressed "serious reservations on how [the proposed drug distribution system] is currently described in terms of assuring safe and adequate credentialing of providers."[221] The Committee recommended additional restrictions designed to ensure "that this drug not be expanded to hands of physicians who are not already skilled in managing pregnancies, terminations, and complications of both."[222] Accordingly, FDA's 1996 Approvable Letter required the submission of "a comprehensive description of the proposed distribution system."[223]

In subsequent submissions, however, the Population Council insisted that the drug was safe and proffered restrictions designed primarily to control the manufacturing and retailing of the drug product. On August 18, 1999, the Population Council proposed to:[224] (i) limit the number and type of distributors; (ii) limit distribution to distributor-registered physicians who

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[219] In Europe, for example, mifepristone is used under more highly controlled conditions than were ultimately required in the United States. *See* Amendment to NDA 20-687, International Product Labeling with English Translations (submitted March 21, 2000) (presenting English translation of mifepristone product label, approved July 6, 1999, used in Austria, Belgium, Denmark, France, Germany, Greece, the Netherlands and Spain)[FDA FOIA Release: MIF 000493-506].

[220] Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62].

[221] FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45].

[222] FDA Memorandum, "Highlights of the July 19, 1996 Reproductive Health Products Advisory Committee (AC) Meeting on Mifepristone: Outstanding Issues for FDA to Address" (undated): at 3-4 [FDA FOIA Release: MIF 000534-38].

[223] 1996 Mifepristone Approvable Letter , *infra* Appendix A, at 1.

had provided certain assurances;[225] and, (iii) make available "training materials and information" and medical consultation to health care providers and product information to patients.[226] On January 21, 2000, Danco opined that "[r]egardless of the distribution system for mifepristone, the medical safety of this drug is well documented."[227] and proposed a distribution system that was designed only to ensure that Danco would "exert[ ] positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient."[228]

In reaction to the sponsor's recalcitrance, FDA took the position "that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[229] The agency nevertheless continued to encourage the sponsor to take an active role in devising appropriate restrictions on the use of mifepristone. Instead, in March 2000, the Population Council again protested that such restrictions were unwarranted.[230] It submitted a

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[224] *See* Medical Officer's Review, *infra* Appendix A, at 21-23 (setting forth the Population Council's complete response submitted to FDA on August 18, 1999).

[225] The physician would be required to provide a *self*-attestation covering the physician's ability to accurately date pregnancies and determine the patient's blood Rh factor and the physician's access to emergency medical facilities. Registering physicians would also agree to obtain from each patient an acknowledgement that she has received full information and is willing to comply with the treatment regimen, to maintain certain records (including ultrasound and blood test records) for each patient, to report adverse events and information about ongoing pregnancies, and to "[u]se every effort to ensure patients return for their follow up visit 14-20 days after taking the product." *See* Medical Officer's Review, *infra* Appendix A, at 22-23.

[226] *See* Medical Officer's Review, *infra* Appendix A, at 23.

[227] Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26]. Danco attempted to attribute any deleterious effects of mifepristone abortions to misoprostol: "More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin." *Id.* at 2.

[228] *See* Amendment 039 to the NDA, Mifeprex Distribution Plan Executive Summary (Jan. 21, 2000): at 3 [FDA FOIA Release: MIF 000530-31].

[229] *See* 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5. *See supra* Section III.C.2 and III.D. for a discussion of Subpart H, Section 314.520, which is reserved for drugs that are so inherently dangerous that their distribution and use must be restricted.

[230] In the course of objecting to the approval of the drug under subpart H, which is "likely to falsely 'mark' mifepristone as a highly toxic and risky drug," the Population Council insisted that "the FDA knows, [Mifeprex] is

distribution plan that it characterized as "detailed and comprehensive" and "surely equal to its purpose."[231] Once again, the plan consisted of restrictions intended only to control the manufacturing and retailing of the drug product.[232] Again FDA objected that "[t]he proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient."[233] The agency requested "that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product."[234]

On June 1, 2000, FDA proposed the following set of "Qualifications for Physician Recipients:" (1) the physician must demonstrate that she is licensed to practice medicine; (2) the physician must be "trained and authorized by law" to perform surgical abortions; (3) the physician must have "been trained to and ha[ve] the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination;" (4) the physician must have "satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications;" and

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exceptionally safe and effective." Responses by Population Council to "FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)" (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24]("March 2000 Response").

[231] March 2000 Response, *infra* Appendix A, at 2.

[232] Specifically, the plan provided for "secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements." March 2000 Response, *infra* Appendix A, at 2.

[233] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1 [FDA FOIA Release: MIF 007811-13].

[234] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1. FDA wanted the sponsor to provide a set of auditable provider qualifications, a plan for auditing providers to ensure that they were meeting these criteria, and an arrangement for discontinuing distribution to unqualified providers. *See id.* at 2.

(5) the physician must have "continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility."[235] FDA's proposals were intended to address concerns about the safety of the women undergoing mifepristone-misoprostol abortions that the Population Council and Danco had refused to take into account in crafting restrictions for the drug.[236]

The Population Council and Danco objected strenuously to the proposed restrictions and aired their complaints in public.[237] FDA reprimanded the Population Council for leaking the restrictions to the public and misrepresenting the nature of the restrictions.[238] The Executive Vice President of the American College of Obstetricians and Gynecologists submitted an analysis of the leaked restrictions to FDA.[239] The editorial and political reaction,[240] together with the

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[235] *See* FDA, "FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00" (June 1, 2000)[FDA FOIA Release: MIF 000522]. *See also* American College of Obstetricians and Gynecologists, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000): at 1 (setting forth FDA's second proposed restriction, which is redacted in the publicly available copy of FDA's proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

[236] It should be noted, that even these restrictions would not have been sufficient to make mifepristone-misoprostol abortions safe. Among the key safeguards missing from FDA's proposal were requirements that every prospective patient undergo an ultrasound and that prescribing physicians be required to have admitting privileges at facilities able to provide emergency care.

[237] Paul Blumenthal, M.D., Jane Johnson, and Felicia Stewart, M.D., "The Approval of Mifepristone (RU486) in the United States: What's Wrong with this Picture?" *Medscape Women's Health* 5 (2000) (reproduced in an internal FDA email)[FDA FOIA Release: MIF 00002597-99] ("At a meeting of early abortion providers and abortion advocates, the Population Council and Danco revealed that the U.S. Food and Drug Administration (FDA) had made a series of proposals regarding the labeling and distribution of mifepristone that would severely limit women's access to the drug if and when it is approved.").

[238] *See* Teleconference Meeting Minutes (between FDA staff and representatives of the Population Council and Danco) (June 7, 2000): at 1 ("Meeting Objective: . . . to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.")[FDA FOIA Release: MIF 002136-37]; FDA internal email (June 23, 2000): at 1 (re: telephone conversation with Population Council attorney, Nancy Buc, on 6/23/00) ("I also said that we were looking to Pop Council to be a responsible entity in manufacturing, distributing, and shepherding this drug and that most responsible entities make proposals rather than expect FDA to write labels and distribution systems and obtain comments through the media.")[FDA FOIA Release: MIF 002523].

[239] *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) to Jane Henney, M.D. (July 24, 2000) and enclosure: ACOG, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000)[FDA FOIA Release: MIF 001366-69]. ACOG and the American Medical Association ("AMA") also attempted to secure a meeting with

impending approval deadline of September 30, 2000,[241] however, had the desired effect of undermining FDA's resolve.

At a meeting on July 19, 2000, FDA yielded to the Population Council and Danco on a number of important issues.[242] FDA abandoned its proposal for auditable physician qualifications and agreed instead to permit physicians to attest to their own qualifications.[243] Instead of requiring formal training, FDA merely "request[ed] that the physician also attest to having read and understood the training materials and labeling."[244] FDA also agreed not to

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Dr. Jane Henney, FDA Commissioner, and her staff, in order to further discuss their opinion of the restrictions. *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) and E. Ratcliffe Anderson, Jr., M.D. (Executive Vice President, AMA) to Jane Henney, M.D. (July 24, 2000): at 1 ("The undersigned organizations . . . are very concerned about restrictions . . . [FDA] has proposed for . . . mifepristone. . . . We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely from political influence.")[FDA FOIA Release: MIF 001363]. They were permitted only to meet with officials in FDA's Office of Women's Health, an office within the agency that was not involved in reviewing the NDA. *See* Letter, Jane Henney to Hale and Anderson (Aug. 11, 2000): at 1-2 [FDA FOIA Release: MIF 001361]. The questionable scientific basis for this challenge to FDA's proposed restrictions was recently brought to the attention of ACOG by one of the Petitioners. Letter, Donna Harrison, M.D. (Chairperson, AAPLOG Committee on Mifeprex Use) to Ralph Hale, M.D. (Executive Vice President, ACOG) (May 23, 2002) (available at <http://www.aaplog.org/acogmifeprexletter.htm>).

[240] *See, e.g*, Letter, U.S. Senator Barbara Boxer to Dr. Jane Henney (June 9, 2000): at 1 ("According to news reports, the FDA is considering placing draconian restrictions on the accessibility of RU-486 as a condition of its approval . . . . In 1996, the FDA found RU-486 to be safe and effective. Therefore, it is a mystery to me why the FDA would even consider restricting access to it.")[FDA FOIA Release: MIF 006376]; Letter, Mark Green, Public Advocate for the City of New York, to Dr. Jane Henney (Sep. 22, 2000): at 1 ("Earlier this week Planned Parenthood of New York City, NARAL-New York, the Access Project and Physicians for Reproductive Health and Choice joined me in convening a public hearing in New York City on pending action by [FDA] on mifepristone . . . . [I am] also concerned about the restrictions on access to RU-486 that FDA is said to be considering.")[FDA FOIA Release: MIF 001288-1302]; Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times* (June 8, 2000): at A21 ("The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by [FDA] that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it."); Letter, U.S. Representative Lynn Woolsey to Dr. Jane Henney (June 22, 2000): at 1 ("However, I am deeply concerned about recent press reports about proposed restrictions.") [FDA FOIA Release: MIF 006372].

[241] As noted above, because FDA had accorded priority review to mifepristone, the approval process was slated for completion by September 30, 2000.

[242] *See* Meeting Minutes, re: Approvability Issues Related to Labeling and Distribution Plan for Mifepristone (July 19, 2000): at 2-4 [FDA FOIA Release: MIF 004661-65].

[243] *See id.* at 2.

[244] *Id.* at 2.

require pre-procedure ultrasounds.[245] Furthermore, FDA stated "that it is not necessary to require the patient to take the drugs in the presence of health care provider."[246]

Among the unresolved issues at the conclusion of the July 19, 2000 meeting was the question of whether prescribing physicians should be limited to those who were able to perform surgical abortions, a provider qualification FDA believed was necessary:

> FDA requests that the ability to perform vacuum aspirations and/or D&Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women's health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.[247]

The Population Council later rejected FDA's request,[248] and the agency acquiesced.[249]

Despite its persistent concerns, FDA approved a regimen that posed the very risks to women's health that the agency had previously identified. When it approved Mifeprex, FDA stated that "[u]nder 21 CFR 314.520, distribution of the drug is restricted as follows:"

> Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through 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™.

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[245] *See id.* at 3.

[246] *Id.* at 3.

[247] *Id.* at 3.

[248] *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 6 (arguing that bolstering the provider qualifications in this way would be "not only unnecessary, but also in fact potentially counterproductive for patients")[FDA FOIA Release: MIF 0001373-81].

[249] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 [FDA FOIA Release: MIF 004587-88].

- 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, 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.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- 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 records.[250]

In addition, the restrictions include a requirement that distribution be carried out in accordance with the plan submitted to FDA by the Population Council in a March 30, 2000 submission.[251] Even as it assented to a regimen that lacked critical safeguards, FDA took a number of steps that indicated its lingering concerns about the safety of the drug. First, FDA ultimately decided to rely on an infrequently used provision in Subpart H in hopes of ensuring that mifepristone would be used safely and, if necessary, could be withdrawn from market rapidly.[252] Second, the staff insisted that the mifepristone label "include a black boxed warning describing the major requirements and conditions for use."[253] "FDA generally reserves boxed warnings for serious or

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[250] Mifeprex Approval Letter at 2.

[251] *See* Mifeprex Approval Letter at 2.

[252] *See* 21 C.F.R. 530 ("Withdrawal Procedures"). *See also* FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85]. As late as July 19, 2000, the question of whether to use Subpart H was deemed to be an "Outstanding Issue." *See* Meeting Minutes, re: Approvability Issues (July 19, 2000): at 4 [FDA FOIA Release: MIF 004661-65].

[253] FDA, Memorandum, re NDA 20-687 (Feb. 17, 2000): at 2. The Population Council, which opposed the inclusion of such a warning, ultimately persuaded FDA to agreed to a pared-down Black Box Warning, which would merely direct the prescribing physician (i) to plan in advance for emergency care, and (ii) to make available to the patient and provide her with the opportunity to discuss the patient information and patient agreement. *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 1-2 [FDA FOIA Release MIF 0001373-81].

life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner."[254]

FDA's willingness to tailor the restrictions on Mifeprex to suit the demands of the Population Council and Danco will continue to manifest itself in serious adverse events among the women who use the Mifeprex Regimen. Some of the most critical flaws in the approved regimen are discussed below along with serious adverse events that have already been reported.

1. The Approved Regimen Is Unsafe Because It Does Not Require Ultrasound

a. Ultrasound Is Necessary to Accurately Date Pregnancies

The gestational age of a woman's pregnancy is a critical factor in determining whether she is an appropriate candidate for a mifepristone abortion. In order to minimize the risks of hemorrhage, incomplete abortion and continuing pregnancy, the gestational age of the pregnancy must be less than or equal to 49 days.[255] The authors of the Spitz Article, for example, found that "[f]ailures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of the pregnancy."[256] Through the combination of mifepristone and

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[254] Judith E. Beach et al., "Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs," *Food and Drug Law Journal* 53 (1998): 403-412, at 403 (available at: <http://www.fdli.org/pubs/Journal%20Online/53_3/art2.pdf>). *See also* 21 C.F.R. § 201.57(e) ("Warnings").

[255] As noted above, the gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy.

[256] Spitz Article, *infra* Appendix A, at 1241. "The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the [less than or equal to] 49-days group to 9 percent in the 57-to-63 days group (P<0.001)." Children born from ongoing pregnancies, after a failed application of the Mifeprex Regimen, may suffer birth defects, fertility problems, or other health problems later in life. Researchers have found evidence linking misoprostol and birth defects such as missing or deformed limbs and misshapen skulls. Much of this research was conducted in Brazil, where numerous women have attempted to induce abortions using misoprostol alone. *See, e.g.*, Sylvia Pagán Westphal, "Birth Defects Caused by Ulcer Drug Abortions," *NewScientist.com* (29 Aug. 2001) ("Several studies in Brazil, where up to 75 percent of clandestine abortions involve misoprostol, suggest the drug causes birth defects such as fused joints, growth retardation and a condition known as Möbius syndrome, which is characterised by paralysis of the face."); Iêda M. Orioli and Eduardo E. Castilla, "Epidemiological

misoprostol, "pregnancy was terminated in 762 of the 827 women pregnant for [less than or equal to] 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) . . . ."[257] The study also found that "[a]bdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age."[258] Due to the significant increase in failures and complications with increasing gestational age, FDA approved Mifeprex only for pregnancies of less than or equal to 49 days' gestation.[259]

The only way to date a pregnancy with the degree of accuracy necessary to exclude women whose pregnancies are beyond 49 days' gestation is by use of transvaginal ultrasound. FDA severely undermined the limitation on gestational age, however, when it failed to require

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Assessment of Misoprostol Tetratogenicity," *British Journal of Obstetrics and Gynaecology* 107 (April 2000): 519-23, at 522 (". . . there is an association of prenatal use of misoprostol as an abortifacient and congenital defects of vascular disruption type."); F.R. Vargas *et al.*, "Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case-Control Study," *American Journal of Medical Genetics* 95 (2000): 302-306, at 306 ("add[ing] epidemiological basis to the growing body of evidence that prenatal exposure to misoprostol is related to the occurrence of vascular disruption defects in some exposed fetuses."). FDA determined that data submitted by the Population Council from a survey of fetal abnormalities in 82 pregnancies that were exposed to mifepristone alone or in combination with misoprostol was inconclusive. *See* FDA Mifeprex Approval Memorandum, *infra* Appendix A, at 4. FDA acknowledged, however, the possible link between misoprostol and birth defects. *See* Medical Officer's Review, *infra* Appendix A, at 18 (". . . 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)."). The need for a study of the possible joint effects of mifepristone and misoprostol on babies born after a failed application of the Mifeprex Regimen was highlighted by the abnormalities discovered in a fetus exposed to misoprostol and mifepristone. *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Number 3877547-X (March. 1, 2002) (French report of numerous deformities in fetus that was exposed to mifepristone and misoprostol but survived until a subsequent surgical abortion was performed; "The anatomopathology examination showed a meningo-encephalocele. The left hand was constituted of only two fingers (oligodactylia), left and right foot were constituted of only one finger (monodactylia). There was a facial dysmorphia.").

[257] Spitz Article, *infra* Appendix A, at 1241.

[258] Spitz Article, *infra* Appendix A, at 1241. In order to treat vaginal bleeding, "[t]wo percent of the women in the [less than or equal to] 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids (P=0.008)." *Id.*

[259] FDA's Medical Officer's Review noted: "The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age." Medical Officer's Review, *infra* Appendix A, at 18. The review stated further: "This method of pregnancy termination is of limited value because of the relatively short window of opportunity, 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." *Id.*

the ultrasound dating of pregnancies. FDA's approved regimen relies instead on a patient's recollection of her menstrual history and a physical examination. Dating based on menstrual history is inherently inaccurate because women may not have a perfect 28-day menstrual cycle[260] and because 25 percent of women experience bleeding during the early stages of pregnancy.[261] Gestational dating through physical examination, even when carried out by experienced clinicians, can also be inaccurate.[262] Factors such as patient body size, uterine fibroids, previous parity, and uterine position may impair a clinician's ability to assess uterine size.[263] Transvaginal ultrasound, by contrast, is accurate within plus or minus 3 days at gestational ages of 5 to 7 weeks.[264] "Transvaginal ultrasonographic examination is necessary to ensure accurate gestational

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[260] *See, e.g.,* Leon Speroff, M.D., Robert H. Glass, M.D., and Nathan G. Kase, M.D., *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 219 ("The perfect 28 day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's cycles. Overall, approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days. Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles.").

[261] *See* Peter W. Callen, M.D., *Ultrasonography in Obstetrics and Gynecology* 2nd ed. (Phila, Pa: W.B.Saunders Company; Harcourt, Brace, Jovanovich, 1988) at 32 ("Threatened abortion is a common complication that occurs in approximately 25% of clinically apparent pregnancies."); Speroff, *et al*, *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 536 (noting that "pregnancy and pregnancy-related problems such as ectopic pregnancy or spontaneous abortion" can cause uterine bleeding).

[262] Steven R. Goldstein, M.D., Francis R. M. Jacot, M.D., Claude Poulin, M.D., and D. Scott Poehlmann, M.D., "Documenting Pregnancy and Gestational Age," Chapter 4, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 41 ("Although clinical sizing of the uterus during the first trimester can provide a rough estimate of gestational age, it is imprecise; misestimation of gestational age by uterine sizing alone can occur even in the hands of experienced clinicians.").

[263] *See A Clinician's Guide*, *infra* Appendix A, at 41 ("a number of conditions such as leiomymas, multiple gestation, and obesity may severely limit the accuracy of gestational age assessment by physical examination, warranting preprocedure assessment by ultrasonography in known or suspected cases") (footnotes omitted).

[264] *See* Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," *American Journal of Obstetrics and Gynecology* 168 (March 1993): 903–908; Ivar K. Rossavik, M.D., George O. Torjusen, M.D., and William E. Gibbons, M.D., "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in *in Vitro* Fertilization Pregnancies," *Fertility and Sterility* 49 (1988): 1012-17. *See also* Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and.Gynecology* 180 (1999): 35-41. In this study comparisons of gestational age estimates based on the last reported menstrual period to those generated through ultrasound in patients presenting for medical abortion, revealed the former method to be significantly inaccurate in approximately half the cases. The authors observed: "It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified

dating for provision of medical abortion according to current standards in clinical guidelines established by the National Abortion Federation."[265]

b. Ultrasound Is Necessary to Identify Ectopic Pregnancies

Approximately two percent of all pregnancies in the United States are "ectopic pregnancies," in which the pregnancy is located outside the uterus – often in the fallopian tube.[266] Mifeprex does not terminate ectopic pregnancies.[267] Therefore, if a woman who has an ectopic pregnancy undergoes a mifepristone-misoprostol abortion, she is at risk for tubal rupture and subsequent hemorrhage due to delay in diagnosis and delay in treatment. The symptoms of an ectopic pregnancy – vaginal bleeding, pelvic pain, and cramping – are confusingly similar to certain side effects of the Mifeprex Regimen.[268] A woman with an ectopic pregnancy is at risk of suffering massive intra-abdominal hemorrhage, damage to her reproductive organs, permanent

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by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present . . . . These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included." *Id.*

[265] Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and Gynecology* 180 (1999): at 35-41 (text preceding n. 8) (citation omitted).

[266] Centers for Disease Control, "Ectopic pregnancy – United States, 1990-1992," *Morbidity and Mortality Weekly Report* (*MMWR*) 44 (No. 3) (Jan. 27, 1995): at 46. The number of ectopic pregnancies may be even higher now because sexually transmitted diseases and other causes of ectopic pregnancy are more widespread than they were in 1992 – the latest year for which the Centers for Disease Control have reported the number of ectopic pregnancies. *Id.* at 46-7.

[267] *See, e.g.*, Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-S75, at S72 ("Mifepristone has not proved effective in treating extrauterine pregnancy . . . .").

[268] *See* American College of Obstetricians and Gynecologists, "Medical Management of Abortion," *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists* 26 (April 2001): at 6 (noting that in medical abortions, "women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy") ("ACOG Practice Bulletin"). Vaginal bleeding, for example, is a normal consequence of the Mifeprex Regimen and may continue for weeks after a woman ingests Mifeprex and misoprostol. *See, e.g.*, Spitz, *infra* Appendix A, at 1243 ("Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated

sterility, and even death if not promptly treated by emergency surgery. The authors of a French mifepristone study in which a participant with an ectopic pregnancy underwent emergency surgery to stop heavy bleeding, concluded that:

> The case of undiagnosed ectopic pregnancy, which ruptured suddenly 2 days after misoprostol intake, indicates that (1) mifepristone plus misoprostol is not an effective treatment of ectopic pregnancies and should not be used for this purpose, and (2) all medical means of detecting an ectopic pregnancy should be used before prescribing mifepristone plus misoprostol.[269]

Although the Mifeprex Label states that the Mifeprex Regimen is contraindicated for women with a "[c]onfirmed or suspected ectopic pregnancy,"[270] FDA did not require that ultrasound be used to exclude women with ectopic pregnancies. Instead, the approved regimen relies solely on a self-certification by the prescribing physician that she has the "[a]bility to diagnose ectopic pregnancies."[271] A physical examination alone cannot accurately identify ectopic pregnancies. Ultrasound, "[i]n addition to providing the best information for gestational age determination . . . can also provide useful diagnostic information regarding a wide variety of pathologies of early pregnancy," including ectopic pregnancies.[272]

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medically. The median duration of bleeding or spotting was 13 days in the [less than or equal to] 49-days group and 15 days in the other two groups (P<0.001).").

[269] Elizabeth Aubény, *et al.*, "Termination of Early Pregnancy (Up to 63 Days of Amenorrhea) with Mifepristone and Increasing Doses of Misoprostol," *International Journal of Fertility & Menopausal Studies* 40 (1995): 85-91, at 91.

[270] *See* Mifeprex Label ("Contraindications").

[271] *See* Mifeprex Prescriber's Agreement.

[272] *A Clinician's Guide*, *infra* Appendix A, at 47-8.

2. FDA's Approved Regimen Is Not Restricted to Properly Trained Physicians who Have Admitting Privileges to Emergency Facilities

FDA's approved regimen lacks any objective qualifications for prescribing physicians and administering health care providers.[273] The health care provider administering the Mifeprex Regime need not undergo training, may not necessarily be an obstetrician or gynecologist, may not have any surgical training or training in the management of abortion complications, and may not even be a physician.[274] For example, the Mifeprex Regimen could be administered by a nurse untrained in any type of abortion and under the remote supervision of a family practitioner who does not regularly practice obstetrics and is incapable of providing emergency care.

Physicians and the health care staff that they supervise require formal training in both pharmaceutical and surgical abortion to minimize the morbidity inherent in performing mifepristone abortions.[275] National Abortion Federation guidelines provide that "[a]ll personnel performing abortions must receive training in the performance of abortions and in the prevention,

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[273] Self-certifications do not provide an effective substitute for imposing objective, auditable requirements. The Mifeprex Prescriber's Agreement, for example, merely requires that the prescribing physician profess to have the "[a]bility to assess the duration of pregnancy accurately." The vacuity of this stipulation is illustrated in remarks made by Dr. Susan Allen (who later became an FDA official) before the FDA Advisory Committee. Dr. Allen stated, "If you also recall when you go through medical school you learn how to date a pregnancy." FDA Hearings Transcript, *infra* Appendix A, at 319.

[274] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 ("the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners")[FDA FOIA Release: MIF 004587-88]; *see also*, Mifeprex Approval Memo, *infra* Appendix A, at 4-5 ("Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician from dispensing the drug to patients, provided state laws permit this.").

[275] A survey of methotrexate abortion providers underscores the necessity of training in both medical and surgical abortion. *See* S. Marie Harvey, Linda J. Beckman, and Sarah J. Satre, "Experiences and Satisfaction with Providing Methotrexate-Induced Abortions among U.S. Providers," *Journal of the American Medical Women's Association* 55 (2000): 161-63, at 162 (In a study comparing methotrexate and surgical abortion, "[m]ost providers felt strongly that all clinic staff should be familiar with both procedures and, thus, the training needs would be equivalent. This thought was echoed not only by physicians, who must be prepared to perform an emergency surgical abortion if methotrexate fails, but also by other clinic personnel. Thirty-nine percent of providers thought that medical abortion

recognition, and management of complications."[276] Additionally, ACOG recommends that "[c]linicians other than obstetrician-gynecologists who wish to provide medical abortion services should work in conjunction with an obstetrician-gynecologist or be trained in surgical abortion in order to offer medical abortion treatment."[277] The necessity for training in surgical abortion as well as mifepristone abortion stems primarily from the high failure rate of the Mifeprex Regimen. In the U.S. Clinical Trial, the Mifeprex Regimen failed for 8 percent of women with pregnancies of less than or equal to 49 days' gestational age.[278]

Excessive bleeding, which is much more common following a Mifeprex abortion than a surgical abortion, is particularly likely to necessitate urgent surgical intervention. Based on an international study comparing surgical and medical abortion, FDA's Medical Officer noted that "[o]n the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients" and characterized this as a "serious potential disadvantage of the medical method."[279] In the U.S. Clinical Trial among patients whose pregnancies were of no more than 49 days' gestation, excessive bleeding resulted in one blood transfusion, two hospitalizations, two emergency room treatments, and thirteen surgical interventions.[280] In

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required more training; specifically, learning to do a vaginal ultrasound and to handle the unpredictable outcomes of methotrexate abortion required lengthy training.").

[276] National Abortion Federation, "National Abortion Federation Clinical Policy Guidelines, 1998," Appendix, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999): at 256 ("*A Clinician's Guide*").

[277] ACOG Practice Bulletin, *infra* Appendix A, at 6.

[278] *See* Medical Officer's Review, *infra* Appendix A, at Table 1. Seventeen percent of women with pregnancies of between 50 and 56 days' gestational age and 23 percent of women with pregnancies between 56 and 63 days were failures. *See id.* In an international study reviewed by the Medical Officer, failure rates for mifepristone abortion were 5.2 percent, 8.6 percent and 16 percent in India, China and Cuba respectively, while comparable failure rates for surgical abortion were 0, 0.4 percent, and 4.0 percent. *See* Medical Officer's Review, *infra* Appendix A, at 19.

[279] Medical Officer's Review, *infra* Appendix A, at 19 (no citation by FDA Medical Officer).

[280] Medical Officer's Review, *infra* Appendix A, at 17.

addition, 5 percent of the patients in this group received uterotonic agents to stem bleeding.[281] A delay in intervention may be life-threatening,[282] as was illustrated by the experience of one of the participants in the U.S. Clinical Trial. The treating physician described the incident to the FDA Advisory Committee:

> In November of 1994, I was called to the [emergency room] for a woman who was bleeding due to a miscarriage, and was in obvious shock. A blood test showed that she had lost between one-half to two thirds of her blood volume . . . .
>
> I had thought she was having an incomplete miscarriage, but her husband . . . told me that she had taken RU486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate [dilation and curettage].
>
> Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.
>
> Even later that evening, . . . [s]he required two more units of blood because she was still orthostatic and symptomatic.[283]

The Mifeprex Regimen is contraindicated for "any patient who does not have adequate access to medical facilities equipped to provide emergency treatment."[284] FDA's approved regimen, however, does not require prescribing physicians to have *admitting* privileges to emergency facilities. The approved regimen requires only that a physician who is not able "to provide surgical intervention in cases of incomplete abortion or severe bleeding . . . ma[k]e plans to provide such care through others, and [be] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[285] Plans for back-up care

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[281] Medical Officer's Review, *infra* Appendix A, at 17.

[282] When surgery is indicated because of acute bleeding, significant, or even life threatening blood loss, has already taken place. The preoperative preparation of the patient is often compromised in the rush to complete the surgery, which results in higher infection rates and more anesthetic complications, such as aspiration during intubation.

[283] FDA Hearings Transcript, *infra* Appendix A, at 223-25 (testimony of Dr. Mark Louviere).

[284] *See* Mifeprex Label ("Contraindications").

[285] Mifeprex Prescriber's Agreement. FDA, however, took two steps that suggested that it has lingering concerns about the absence of a surgical intervention qualification for Mifeprex prescribers. First, the Mifeprex Label includes a "black box" warning governing surgical back-up. Second, FDA required the Population Council to perform a post-approval study "[t]o ensure that the quality of care is not different for patients who are treated by

may be nothing more than "having the ability and responsibility to direct patients to hospitals, if needed."[286] Moreover, the approved regimen does not include an objective geographical limitation to ensure that the patient has easy access to the designated emergency care facility.[287]

3. The Sponsor's Recent "Dear Doctor Letter" and FDA's Explanatory Webpage Announcing Serious Adverse Events Validate the Petitioners' Concerns

On April 17, 2002,[288] Danco, with FDA's assistance, issued a letter to health care providers to alert them to "New Safety Information," to remind them that Mifeprex was approved for use in a prescribed regimen, and to encourage them to provide patient counseling and report adverse events.[289] The "New Safety Information" consisted of a number of reports of serious adverse events that had been experienced by women who were undergoing or had

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physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention . . . ." Mifeprex Approval Memo, *infra* Appendix A, at 5.

[286] Mifeprex Approval Memo, *infra* Appendix A, at 5. FDA's decision not to include a requirement that the prescribing physician have admitting privileges at a hospital could delay the patient's admission for emergency care. Another likely consequence of not requiring the prescribing physician to have admitting privileges is underreporting of serious adverse events related to the Mifeprex Regimen. The treating physician, not privy to the Prescriber's Agreement, may not file a serious adverse event report or notify the abortion provider of the complications that arose from the Mifeprex Regimen.

[287] The Chinese experience with mifepristone suggests that mifepristone should not be administered in facilities unable to provide potentially necessary emergency services. Thus, recently, the Chinese State Drug Administration responded to concerns that women were suffering as a result of lax controls on mifepristone by reiterating its policy that the drug "can only be administered at a hospital under a doctor's supervision and cannot be sold at pharmacies even with a prescription." *See* Kaiser Family Foundation, "China Reaffirms Restrictions on Unsupervised Mifepristone Use," *Kaiser Daily Reproductive Health Report* (Oct. 15, 2001) (available at: <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=7453>) (reporting also that, "[t]hree years ago, the Shanghai Health Bureau restricted the use of mifepristone to certain hospitals in the area because of fears of complications").

[288] The letter bears the date, April 19, 2002, but was disseminated to the public on April 17, 2002.

[289] Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) ("Dear Doctor Letter") (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>). Coincidentally, on the same day FDA and Danco publicized these serious adverse events, the agency also announced major changes to the Cytotec (misoprostol) label. *See* FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). Pursuant to these labeling changes, pregnancy was removed from the list of contraindications on the Cytotec label and the black box warning cautioning pregnant women not to take the drug was also removed.

recently completed the Mifeprex Regimen.[290] A number of patients had suffered from ruptured ectopic pregnancies and one of these women died from hemorrhage.[291] The letter also reported "[t]wo cases of serious systemic bacterial infection (one fatal)."[292] The fatality apparently precipitated a halt in the Population Council's Canadian clinical trials of mifepristone.[293] Finally, a 21 year old woman suffered a heart attack three days after she completed the Mifeprex Regimen.[294] These and other adverse events had been reported to FDA through its Adverse Event Reporting System (AERS).[295] Two of the patients who were reported to have suffered life-threatening adverse events were 15 years old.[296] These incidents bear out the concerns about the safety of the regimen detailed above, and the relatively high rate of serious adverse events among adolescents is of particular concern.

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[290] The letter did not specify the number of adverse events about which Danco had been informed, but five individual cases were discussed.

[291] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[292] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[293] It appears that the woman reported to have died from a systemic bacterial infection was a Canadian trial subject. *See* Marnie Ko, "A Volunteer Dies While Testing a Controversial New Drug, Bringing the Trial to a Halt," The Report (Oct. 8, 2001) (available at: <http://report.ca/archive/report/20011008/p48ai011008f.html>). *See* also Henry P. Kaiser Family Foundation, "Population Council Announces Death of Woman Involved in Canadian Mifepristone/Misoprostol Trial," Daily Reproductive Health Report (Sept. 11, 2001) (available at: <http://www.kaisernetwork.org/Daily_reports/rep_index.cfm?DR_ID=6877>). A *Clostridium sordellii* infection apparently caused the woman to suffer septic shock. *See generally* G.L. Mandell, J.E. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases* (5th ed. 2000): at 2551 (explaining that a disease process in which "clostridia clearly play a major pathogenic role i[s] uterine gas gangrene, now a rare complication that was previously seen in the setting of septic abortion." "*C. sordellii* has been reported as a cause of uterine gas gangrene . . . ."). *See also* FDA Q & A's, *infra* Appendix A, at Question 3 ("Serious systemic bacterial infection is a severe life-threatening infection that spreads throughout the body and can cause death.").

[294] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[295] *See, e.g.*, Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3819498-2 (Nov. 2, 2001) (intervention to prevent permanent impairment or damage); 3806144-7 (Oct. 9, 2001) (death of a patient with an ectopic pregnancy); 3769840-6 (July 30, 2001) (hospitalization of patient with an ectopic pregnancy); 3769842-X (July 30, 2001) (intervention to prevent permanent impairment or damage); 3719885-7 (May 8, 2001) (death in conjunction with the use of misoprostol and Mifegyne, which is the trade name of mifepristone distributed in France); 3713452-7 (Apr. 27, 2001) (intervention to prevent permanent impairment or damage); and, 3769838-8 (July 30, 2001) (intervention to prevent permanent impairment or damage). The AERS depends on voluntary reporting and the accuracy of these reported adverse events cannot be verified, nor can the cause of these events be identified with certainty. There may have been other adverse events that were not reported.

Simultaneously with Danco's distribution of the *Dear Doctor Letter*, FDA published a webpage with 14 questions and answers related to mifepristone in an attempt to answer some of the questions likely to be prompted by the letter and to urge health care providers to adhere to the approved regimen.[297] FDA's answers, however, leave much to be desired from a medical and scientific standpoint.

First, FDA has understated the possibility that the Mifeprex Regimen caused the serious adverse events reported in the letter.[298] FDA did not adequately explain why women who were apparently healthy prior to undergoing the Mifeprex Regimen experienced life-threatening or fatal complications such as ruptured ectopic pregnancies, heart attacks, and systemic bacterial infections.

Second, FDA inappropriately attempted to link these adverse events to the unapproved vaginal administration of misoprostol.[299] It was reckless for FDA to suggest that the vaginal administration of misoprostol caused these adverse events while overlooking critical flaws in the

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[296] *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3803789-5 (Oct. 3, 2001) and 3815629-9 (Oct. 26, 2001).

[297] FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm).

[298] *See* Dear Doctor Letter, *infra* Appendix A, at 1 ("No causal relationship between any of these events and use of Mifeprex and misoprostol has been established."). An FDA official interviewed (without attribution) downplayed the connection between the Mifeprex Regimen and the adverse events. *See* Susan Okie, "Physicians Sent Abortion Pill Alert: Six Women Using RU-486 Taken Ill, and Two Died, Letter Says," *Washington Post* (Apr. 18, 2002): at A2 ("These are, in fact, a very small number of events. Some of them were clearly not caused by the drug regimen.").

[299] The repeated references to the unapproved vaginal use of misoprostol in the FDA Q & As give rise to the inference that the reported adverse events are attributable to this single departure from the Mifeprex Regimen. *See, e.g.*, FDA Q & As, *infra* Appendix A, at Question 1 ("In all of these cases, misoprostol was given vaginally, not orally, which is the approved regimen. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol."); *id.* at Question 4 ("We do not know what role, if any, Mifeprex and 'off-label' use of vaginal misoprostol may have in developing serious infections."); *id* at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses? There are published studies of the use of mifepristone with vaginal administration of misoprostol for abortion. The misoprostol doses used in these studies are higher than those described in the Mifeprex labeling . . . ."); *id.* at Question 10 ("Are there risks with vaginal use of misoprostol?").

approved regimen for Mifeprex use in the United States. FDA should have first assessed essential aspects of this regimen.

It is clear, for example, that absent ultrasonographic screening for ectopic pregnancy, there is increased risk that an intact or rupturing ectopic pregnancy will be misdiagnosed as a normally progressing Mifeprex abortion. Additionally, Mifeprex abortions may be performed by practitioners who are not physicians, who cannot perform surgical abortions, or who are unable to diagnose ectopic pregnancies and their complications.

Nor is there reason to believe that systemic bacterial infection is more likely to occur following vaginal, rather than oral, administration of misoprostol. Misoprostol is commonly administered vaginally for the induction of labor without higher reported rates of either intrauterine or systemic infection when compared to orally administered misoprostol or other methods of labor induction. Rather, the occurrence of life-threatening infection in women undergoing a Mifeprex abortion should raise questions about whether prolonged genital tract bleeding in the artificial hormonal milieu created by the Mifeprex Regimen might foster or promote infectious complications. In addition, infection might occur in women who, believing that their abortion is complete and unaware that their uterus actually contains dead tissue, fail to return for follow-up visits.[300] This may be a particular problem when the Mifeprex Regimen is prescribed to adolescents.

The occurrence of a heart attack in a 21 year old woman is always cause for significant concern. A French woman undergoing a mifepristone abortion suffered a fatal heart attack in

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[300] A. Karen Kreutner, M.D., "Postabortion Infections," *Contemporary Ob/Gyn* 1 (2001): at 37-42 (". . . because medical termination may be incomplete in between 3% and 23% of patients, retained tissue and subsequent infection may go unrecognized in those lost to follow up. . . . Some experts fear there will be compliance problems with the third visit, especially when the patient terminates early. In these cases, retained tissue, thought by the patient to be normal bleeding, could lead to endometritis.").

1991. A different prostaglandin (Sulprostone) administered by injection was used in that case.[301] This new case highlights the need for further investigation into a possible causal link between mifepristone-prostaglandin abortions and myocardial infarction.[302]

The ratio of serious adverse events to total uses of the Mifeprex Regimen cannot be ascertained because serious adverse event reporting is likely incomplete and because it is not publicly known how many times the Mifeprex Regimen has been used. Regardless of the relative number of serious adverse events, the nature of these events demands immediate FDA action to prevent future patient injuries and deaths.[303] The Joint Commission on the Accreditation of Healthcare Organizations[304] ("JCAHO" or "Joint Commission") has developed an approach for investigating adverse events similar in gravity to those that prompted the issuance of the Dear Doctor Letter. The JCAHO looks for "sentinel events" which are "unexpected occurrence[s] involving death or serious physical or psychological injury, or the risk thereof."[305] "Sentinel events" *signal* the need for the commencement of a "root cause

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[301] *See* "Noticeboard: A Death Associated with Mifepristone/Sulprostone," *Lancet* 337 (April 20, 1991): at 969-70 ("A spokeswoman for Roussel-Uclaf SA, the company that manufactures mifepristone, said 'the death was clearly from cardiovascular shock following 'Nalador' (Schering) injection.'").

[302] The Mifeprex Regimen should be contraindicated for women with cardiovascular risk factors until further clinical experience indicates that such contraindication is unnecessary.

[303] Even FDA acknowledged the rarity of the events referenced in the Dear Doctor Letter. With respect to bacterial infection, for example, FDA observed that "the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1-4.7% of first trimester surgical abortions and in 0.0-6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth." FDA Q & A's, *infra* Appendix A, at Question 3. FDA similarly noted the unusual nature of a heart attack in a young woman: "The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare. . . . In 1997, the rate among US women aged 20-24 years was 0.19 per 100,000 women." *See id.* at Question 4.

[304] The Joint Commission "evaluates and accredits nearly 18,000 health care organizations and programs in the United States. An independent, not-for-profit organization, JCAHO is the nation's predominant standards-setting and accrediting body in health care. Since 1951, JCAHO has developed state-of-the-art, professionally based standards and evaluated the compliance of health care organizations against these benchmarks." Joint Commission webpage at: <http://www.jcaho.org/whatwedo_frm.html>.

[305] Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#I. Sentinel Events>.

analysis" of the event(s),[306] with the goal of developing an appropriate administrative response from the health care organization that will prevent the occurrence of future serious adverse events. A root cause analysis of sentinel events is performed before a statistically significant number of injuries or deaths occurs. It seeks to discern the facts surrounding each occurrence, distinguish factors peculiar to individuals from those pointing to procedural or administrative deficiencies, and recommend corrective measures to such systemic failures in the delivery of a particular therapy.

It is particularly important that FDA react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA's endorsed scientific methodology for such trials. The substandard trial design of the U.S. and French Clinical Trials precluded an accurate estimation of the safety of the Mifeprex Regimen compared to the existing available alternatives. Moreover, FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data. The agency has not performed a root cause analysis, but has instead hastily postulated that the vaginal administration of misoprostol is the underlying cause of the adverse events.[307] The Petitioners believe that there are probably more scientifically sound explanations for these adverse events and that the supposed safety of the Mifeprex Regimen has been called into question. The occurrence of the adverse events related to ectopic pregnancies and life-threatening systemic bacterial infections adds significant weight to the concerns of those

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[306] The Joint Commission defines "root cause analysis" as "a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event. A root cause analysis focuses primarily on systems and processes, not individual performance. It progresses from special causes in clinical processes to common causes in organizational processes and identifies potential improvements in processes or systems that would tend to decrease the likelihood of such events in the future, or determines, after analysis, that no such improvement opportunities exist." Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#Root cause analysis>.

who have long warned that mifepristone-misoprostol abortions are dangerous. FDA has previously dismissed such concerns but now must respond to the accumulating evidence and act accordingly. Withdrawal of the approval is warranted.[308]

H. FDA'S APPROVAL OF MIFEPREX SHOULD BE WITHDRAWN BECAUSE THE SPONSOR IS NOT ENFORCING THE LIMITED RESTRICTIONS ON THE USE OF MIFEPREX

Mifeprex abortion providers openly flout the restrictions included in the approved regimen without any reaction from FDA, Danco, or the Population Council.[309] Shortly after approval, FDA asserted that "[i]f restrictions are not adhered to, FDA may withdraw approval."[310] Subpart H authorizes FDA to withdraw approval of a drug approved under Section 314.520 if "[t]he applicant fails to adhere to the postmarketing restrictions agreed upon."[311] When it adopted Subpart H, FDA explained that "[t]he burden is on the applicant to ensure that

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[307] *See* FDA Q & As, *infra* Appendix A, at Nos. 1, 4, 9, 10, and 11.

[308] The Secretary of HHS is authorized by 21 C.F.R. § 314.530(a) to withdraw approval of a Subpart H drug, subject to the applicant's right to a hearing, if, among other things, "(3) [u]se after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug; (4) [t]he applicant fails to adhere to the postmarketing restrictions agreed upon; (5) [t]he promotional materials are false or misleading; or (6) [o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use."

[309] The absence of a reaction from Danco may not be surprising in light of the cavalier attitude towards the FDA approval process exhibited by Dr. Richard Hausknecht, who is Danco's medical director. As early as July 1994, Dr. Hausknecht, had used methotrexate and misoprostol in clinical tests in the U.S. that Dr. Mitchell Creinin, a prominent abortion researcher, described as "downright unethical" and which Sandra Waldman of the Population Council described as being "very risky." Dr. Hausknecht stopped these experiments in September 1994 when the FDA told him to "stop performing the abortions unless he gets the backing of a medical institution and submits his data and procedures to the FDA for review." Carol Jouzaitis, "Doctor's Abortion-Drug Technique Draws Fire," *Chicago Tribune* (Sept. 12, 1994): at 1 & 14. Dr. Hausknecht admitted, " 'This is a little bit uncharted.' . . . . But he declared: 'Damn it. I'm not going to wait. This is a step forward. This is important. I want to see this available to women where it's not available now.' " *Id.* In addition, Dr. Hausknecht's website explains step two of the Mifeprex procedure that he employs: "At the conclusion of the [first] visit, the patient receives a packet containing tablets of misoprostol which are to be taken orally or placed in the vagina depending on the regimen you and Dr. Hausknecht choose." Available at: <http://www.safeabortion.com/procedure.htm> (visited July 7, 2002). Both the home use and the vaginal administration of misoprostol contravene FDA's approved regimen.

[310] *See* Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

[311] 21 C.F.R. § 314.530(a)(4).

the conditions of use under which the applicant's product was approved are being followed."[312] FDA should exercise its authority to withdraw its approval for Mifeprex.

Among the common departures from the approved regimen is the practice of offering the Regimen to women with pregnancies beyond seven weeks.[313] The "Mifepristone Medication Guide" directs women not to take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began." Moreover, women who use the Mifeprex Regimen sign a Patient Agreement, which includes a representation by the patient that "I believe I am no more than 49 days (7 weeks) pregnant.").[314] Thus, the practice of offering Mifeprex to women beyond seven weeks not only contravenes the approved regimen, but it also effectively requires patients to make an untruthful representation in the Patient Agreement. The *Los Angeles Times* explained that, "[B]y offering mifepristone up to the ninth week of pregnancy," Family Planning Associates, "the nation's largest for-profit abortion chain," "obtains a competitive edge over Planned Parenthood, which stays within the seven-week guideline."[315]

In another common deviation from the approved regimen, some abortion providers have eliminated the second of the three prescribed visits. During the initial visit, these providers give

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[312] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[313] Liberty Women's Health Care of Queens, NY, openly acknowledges its use of Mifeprex beyond seven weeks: "While the FDA has approved mifepristone for non-surgical abortions only up to 7 weeks, we use a modified method to extend this period of eligibility in selected patients an additional 14 days up to 9 weeks." Available at: <http://www.abortbypill.com/2.html> (visited Dec. 31, 2001). Likewise, Preterm, an abortion clinic in Cleveland, Ohio, states that abortion using Mifeprex "is effective in terminating pregnancies up to 63 days (9 weeks) from the last normal menstrual period." Available at: <http://www.preterm.org/nonsurg.htm> (visited July 7, 2002).

[314] *See* Item 4 of the Patient Agreement for Mifeprex (mifepristone) Tablets ("Patient Agreement").

[315] Denise Gellene, "RU-486 Abortion Pill Hasn't Caught on in U.S.," *Los Angeles Times* (May 31, 2000): at A1 (quoting Family Planning Associates' official as saying, "You can catch a lot of women in those two [extra] weeks"). Family Planning Associates' website confirmed that the abortion provider offers Mifeprex to women with pregnancies up to nine weeks' gestational age. Available at: <http://www.webworldinc.com/fpamg/abortion_pill.htm> (visited July 7, 2002) ("Medical abortion is limited to patients less than nine weeks pregnant as verified by ultrasound.").

the patient misoprostol, typically with instructions to administer it to herself vaginally[316] at home two days later.[317] Yet home administration of misoprostol runs counter to what patients agree to in the Patient Agreement, which states that "I will . . . return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant."[318] The Population Council argued in favor of and FDA considered the benefits of self-administration at home, chief among which is the reduced burden on abortion providers and their facilities, but the agency concluded that these benefits are outweighed by the significant risks to women.[319] The second visit affords the physician the opportunity to monitor the status of

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[316] The likely reason that FDA's approved regimen calls for oral administration is that it is the only mode of administering misoprostol that is currently approved by the FDA. As discussed above, however, the use of misoprostol in conjunction with mifepristone to effect abortions is itself an unapproved indication.

[317] Presidential Women's Center in West Palm Beach, Florida, for example, gives women "four Misoprostol 200 mcg tablets to take home. Forty eight hours after the Mifepristone tablets have been administered the woman moistens four Misoprostol tablets with tap water and inserts them high into her vagina with her fingers." Available at: <http://www.presidentialcenter.com/medical.html> (visited July 7, 2002). *See also*: <http://www.heritageclinic.com/abortion/medical_abortion_pill.htm> (visited July 4, 2002) (Two days after the patient takes mifepristone, she "inserts Cytotec vaginally, which causes the uterus to contract and expel the embryo. This is very similar to the procedure that was FDA approved in 2000 and is approximately 98% effective. **Note:** The FDA approved protocol calls for 3 Mifeprex pills taken orally the first day and 2 Cytotec pills taken orally two days later. However, subsequent studies have show[n] 1 oral Mifeprex and 4 vaginal Cytotec to be as effective with less gastro-intestinal upset."); *see also*: <http://www.fwhc.org/concord/pages/mifepristone.html> (visited July 7, 2002) (Concord Feminist Health Center's web site describes the second phase of the procedure: "In a few days she inserts misoprostol tablets into her vagina. The pregnancy usually ends at home within four hours."); *see also*: <http://www.gynemed.org/ru.html> (visited July 7, 2002) (Gynemed Surgi-Center's web site states: "You will be given two doses of Misoprostol tablets and instructions on how to insert them into your vagina, which you wil[l] do 48 hours after taking RU486."); *see also*: <http://www.hopeclinic.com/medab.htm> (visited July 7, 2002) (Hope Clinic for Women, Ltd. Explains: "You will receive pills, misoprostol ("miss o pross tul") to take home with you. You will be instructed when to use them; they are placed vaginally."). Even the National Abortion Federation, which initiated a nationwide advertising campaign for Mifeprex, sanctions home administration of misoprostol in its "Medical Abortion Start-Up Packet." *See* National Abortion Federation, "Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 36 ("Home administration of vaginal misoprostol has been found to be safe and effective up to 63 days' gestation and is highly acceptable to patients.").

[318] *See* Patient Agreement, Item 14. *See also* Mifeprex Medication Guide, which explains that on "Day 3 at your provider's office," "your provider will check to see if you are still pregnant," and "[i]f you are still pregnant, take 2 misoprostol tablets."

[319] FDA, which in its 2000 Mifepristone Approvable Letter, agreed to the Population Council's proposal to allow home administration of misoprostol, rejected that option after reconsideration of the issue. *See* Mifeprex Approval Memo, *infra* Appendix A, at 2-3 ("The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the

the termination[320] and assess the need for misoprostol – tasks which cannot be delegated to the patient.[321] In addition, the second visit enables patients whose abortions are complete to avoid having to take misoprostol.[322]

Danco and the Population Council have not effectively constrained providers of Mifeprex to adhere to the approved regimen. It appears instead that Danco and the Population Council have ignored well-publicized departures from that regimen. Deviations from the approved regimen are particularly troubling because the patient is told to disregard the regimen that she reads about in the Medication Guide and pledges to follow in the Patient Agreement. When a drug is approved under Subpart H, the drug's sponsor is responsible for ensuring compliance

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prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. . . . Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.").

[320] Because of the complications that can arise, periodic monitoring during the termination process is important. For the significant percentage of patients that fail to return for the third visit, the second visit may be the last opportunity for a health care provider to monitor the termination. In the U.S. Clinical Trial, five percent of patients failed to return for the third visit. *See* Medical Officer's Review, *infra* Appendix A, at 10. In other studies, the "loss to follow-up has ranged from three to eleven percent." *See* Spitz Article, *infra* Appendix A, at 1246 (citations omitted). The rate of patients who do not complete the entire regimen in routine clinical practice is likely to be even higher as they will not necessarily be subject to the U.S. Clinical Trial's exclusion criteria, which, among other things, excluded women who were "unlikely to understand and comply with the requirements of the study." Medical Officer's Review, *infra* Appendix A, at 9.

[321] *See* ACOG Practice Bulletin, *infra* Appendix A, at 6 (*citing* Mitchell Creinin, *et al.*, "Methotrexate and Misoprostol for Early Abortion: A Multicenter Trial," *Contraception* 53 (1996): at 321-27) ("Women as well as their practitioners are often unable to judge correctly if the women have aborted by evaluating symptomatology. In clinical trials with methotrexate and misoprostol, only about half of women who thought they had aborted actually had done so."); Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-375, S73 ("Studies demonstrate that women may be unable to judge correctly on the basis of symptoms whether abortion has occurred.").

[322] For those patients whose abortions are not complete, the benefits of in-clinic misoprostol use would be enhanced if patients were required to spend several hours afterward in the abortion facility, where they would have ready access to pain medication and other medical help even if the abortion does not occur during the observation period. The Population Council persuaded FDA not to include this requirement, which was included in the protocol for the U.S. Clinical Trial. Forty-nine percent of the participants expelled their pregnancies during the four-hour observation period after the administration of misoprostol. *See* Spitz Article, *infra* Appendix A, at 1243. Nevertheless, a post-misoprostol waiting period was likely disfavored because the protracted presence of large numbers of bleeding and cramping women could place a strain on abortion facilities.

with the restrictions included in the approved regimen for use of the drug.[323] The Population Council and Danco have shirked this responsibility. FDA, therefore, should withdraw its approval of Mifeprex.

I. THE U.S. CLINICAL TRIAL FOR MIFEPRISTONE DID NOT MIRROR THE ANTICIPATED CONDITIONS FOR THE ULTIMATE USE OF THE DRUG

As a general rule, "Phase 3 trials are usually [conducted] in settings similar to those anticipated for the ultimate use of the drug."[324] FDA, however, approved a regimen that does not contain important safeguards that were employed in the U.S. Clinical Trial.[325] In the U.S. Clinical Trial, for example, the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy.[326] The use of ultrasonography also excluded women with ectopic pregnancies. Moreover, physicians participating in the U.S. Clinical Trial had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization.[327] In addition, "[a]ll patients were within one hour of emergency facilities or the

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[323] *See Subpart H Final Rule*, 57 Fed. Reg. at 58953 ("The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed.").

[324] Bertram G. Katzung, M.D., Ph.D., and Barry A. Berkowitz, Ph.D., "Basic & Clinical Evaluation of New Drugs" in Bertram G. Katzung, ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk: Appleton & Lange, 1989): at 56.

[325] The French Clinical Trials, which were not performed by the Population Council, are not discussed here because they were not conducted for the purpose of supporting the mifepristone NDA and, therefore, were not designed to reflect American conditions of use.

[326] *See* Spitz Article, *infra* Appendix A, at 1242.

[327] "The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and /or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists." Mifeprex Approval Memo, *infra* Appendix A, at 5. Medical Officer's Review,

facilities of the principle [*sic*] investigator."[328] In the U.S. Clinical Trial, after taking misoprostol, "women were monitored for four hours for adverse events."[329] FDA has not retained these requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care.[330] FDA should not have extrapolated conclusions about the safety and efficacy of FDA's approved regimen from data generated under trial conditions not mirroring the approved regimen. Effectively, therefore, the agency approved a drug regimen that it had not tested.

J. BY WAIVING THE PEDIATRIC STUDY REQUIREMENT, FDA MAY HAVE ENDANGERED THE HEALTH OF ADOLESCENT GIRLS

FDA's approval of Mifeprex violated FDA's regulations, effective April 1, 1999, requiring that new drugs be tested for safety and effectiveness in the pediatric population (collectively, the "*Pediatric Rule*").[331] Requiring data on girls age 18 and under also would have been consistent with the guidelines for trials in the pediatric population that FDA accepted at the

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infra Appendix A, at 6 (The U.S. Clinical Trial was "conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.").

[328] Mifeprex Approval Memo, *infra* Appendix A, at 5. The "one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services." *Id.* FDA contends that concerns arising from the elimination of the geographical proximity rule have "been dealt with through labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated." Mifeprex Approval Memo at 5.

[329] *See* Spitz Study, *infra* Appendix A, at 1242.

[330] The Prescriber's Agreement requires only that the supervising physician be "able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary." By contrast, the protocol for the U.S. Clinical Trial required that the physician have "privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc." Mifeprex Approval Memo, *infra* Appendix A, at 5. The shift in focus from access by the provider of the abortion to access by the woman who has the abortion, attenuated the link between the abortion provider and the emergency care provider, a link that is critical to ensuring that women receive timely emergency care.

[331] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (*Pediatric Adopting Release*). The notice of proposed rulemaking was released as: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Proposed Rule*, 62 Fed. Reg. 43900 (Aug. 15, 1997).

International Conference on Harmonization.[332] Nevertheless, in the Mifeprex Approval Letter, FDA stated, "We are waiving the pediatric study requirement for this action on this application."[333] Thus, FDA approved Mifeprex for use without requiring safety and effectiveness testing for the pediatric population.[334]

As FDA noted when it adopted the *Pediatric Rule*, "many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established."[335] FDA observed that "the absence of pediatric labeling information poses significant risks for children."[336] The ICH has noted that adolescence "is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development."[337] Such hormonal changes may "influence the results of clinical studies."[338] These concerns for the health of infants, children, and adolescents

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[332] *FDA Guidance: E11 Clinical Testing for Pediatric Uses* at 9 and 11 (Heading for Section 2.5.5). FDA, cognizant of the need for such studies, obtained a commitment from the sponsor in 1996 to conduct Phase IV studies to examine the safety and efficacy of the regimen in girls under 18 years of age. FDA subsequently curtailed this Phase IV study requirement when it approved the Mifeprex NDA.

[333] Mifeprex Approval Letter at 3.

[334] The Mifeprex Label accordingly included the standard disclaimer employed in drug labeling when the drug sponsor has not provided sufficient information to support a pediatric use for the drug: "Safety and effectiveness in pediatric patients have not been established."

[335] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[336] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[337] FDA, "Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population" (Rockville, Md.: Dec. 2000): at 11 (§ 2.5.5) ("*FDA Guidance: E11 Clinical Testing for Pediatric Uses*"). Section 2.5.5 states that the adolescent subgroup should extend from "12 to 16-18 years (dependent on region)." *Id.* at 11-12 (§ 2.5.5).

[338] *See FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 12 (§ 2.5.5). These ICH concerns, quoted below, pertaining to the difficulty of testing drugs in the adolescent population amplify the need for FDA to have required clinical study of the difficulties that might arise when teenage girls undergo the Mifeprex Regimen:

> Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.
>
> Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect

prompted FDA to begin the rulemaking that culminated with the issuance of the *Pediatric Rule*, establishing "a presumption that all new drugs and biologics will be studied in pediatric patients" unless the requirement is waived.[339] More specifically, the *Pediatric Rule* requires that applicants seeking approval for new chemical entities, new biological products, new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration contain safety and effectiveness information on relevant pediatric age groups.[340]

FDA made clear that the Mifeprex NDA was covered by the *Pediatric Rule*.[341] Nevertheless, FDA fully waived the rule for Mifeprex without explanation. Full or partial

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appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol, and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.").

Id. at 12 (§ 2.5.5).

[339] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 (introduction to "II. Highlights of the Final Rule"). The importance of testing drugs in children was highlighted during the recent controversy surrounding FDA's attempt to suspend the *Pediatric Rule*. FDA's planned two-year suspension came in response to the passage of the Best Pharmaceuticals for Children Act, which offers incentives for manufacturers to test drugs in children. Public Law No. 107-109, 115 Stat. 1408 ("BPCA"). *See also* Association of American Physicians and Surgeons, Inc. v. FDA, Defendants' Motion for Stay of Proceedings, Civil Action No. 00-2898 (HHK) (Mar. 18, 2002). FDA later reversed its position in response to criticism from physicians and members of Congress. FDA's attempt to suspend the *Pediatric Rule* prompted the introduction of identical legislation in the House of Representatives and the Senate to codify the *Pediatric Rule*. *See* S. 2394, 107th Congress, 2nd Session (2002) (co-sponsors: Senators Hillary Rodham Clinton (D-NY), Mike DeWine (R-OH), and Chris Dodd (D-CT)); and H.R. 4730, 107th Congress, 2nd Session (2002) (co-sponsors: Representatives John D. Dingell (D-MI), Henry A. Waxman (D-CA), Rosa DeLauro (D-CT), Anna Eshoo (D-CA) and Sherrod Brown (D-OH)). As Senator Hillary Rodham Clinton, a co-sponsor of the Senate bill explained, "if we want to protect our children over the long term, then we in Congress need to step in and make the Pediatric Rule the law of the land. Short of taking that action, we risk denying children the protection that we require for adults." Press Release, "Senators Will Introduce Legislation to Codify Pediatric Rule" (Apr. 17, 2002) (available at: <http://clinton.senate.gov/~clinton/news/2002/04/2002417811.html>). *See also* Marc Kaufman and Ceci Connolly, "U.S. Backs Pediatric Tests In Reversal on Drug Safety," *Washington Post* (April 20, 2002): at A3.

[340] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 ("A. Scope of the Rule"), and as required pursuant to 21 C.F.R. § 314.55(a).

[341] The Mifeprex Approval Letter stated: "Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application." Mifeprex Approval Letter at 3. Because the Mifeprex NDA was filed before the Pediatric Rule went

waivers of the pediatric study requirement may be granted either upon request of the applicant or by FDA on its own motion.[342] Both FDA-initiated and sponsor-requested waivers must satisfy certain criteria. FDA is required to grant a full or partial waiver "if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver … have been met."[343]

Section 314.55 provides three procedural tracks by which an applicant may obtain a waiver of the study requirement. The first requires that two conditions being met: [344] (1)"[t]he drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients," *and* (2) the drug product "is not likely to be used in a substantial number of pediatric patients." With respect to this basis for waiver, FDA has "emphasize[d] that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa."[345] As noted above, FDA, in connection with its determination to approve Mifeprex under Subpart H, concluded that the Mifeprex Regimen provides a therapeutic benefit over the existing treatment – surgical

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into effect, if a waiver had not been granted, the Population Council would have had until December 2, 2000 to submit "an assessment of pediatric safety and effectiveness." *See Pediatric Adopting Release*, 63 Fed. Reg. at 66658-59 ("V. Implementation Plan").

[342] Although it appears that FDA waived the rule *sua sponte*, FDA should have required the manufacturer to provide certain information to support the waiver. The agency has not released such documents to the public in response to FOIA requests. When it adopted the *Pediatric Rule*, the agency noted: "FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request." *Pediatric Adopting Release*, 63 Fed. Reg. at 66648 (§ 29).

[343] 21 C.F.R. § 314.55(c)(4)("FDA action on waiver.").

[344] 21 C.F.R. § 314.55(c)(2)(i).

[345] *Pediatric Adopting Release*, 63 Fed. Reg at 66635 ("II.D.2. Waiver of the Study Requirement," *see* first paragraph).

abortion.[346] This conclusion by itself precludes FDA from using the first method for granting waiver of the *Pediatric Rule*.[347]

Even if FDA had not judged the Mifeprex Regimen to offer a "meaningful therapeutic benefit," the second requirement for waiver in this first track is not met because Mifeprex can be expected to be used in a "substantial number of pediatric patients," which FDA defines as "50,000 pediatric patients with the disease for which the drug or biological product is indicated."[348] In the *Pediatric Adopting Release*, FDA stated that the "relevant age groups will . . . be defined flexibly."[349] With respect to Mifeprex, it would have been appropriate to classify girls under the age of 18 as pediatric patients because safety and effectiveness in this population had not been studied.[350] If the pediatric population comprises all girls age 17 and under, then we estimate that there were 357,200 pediatric pregnancies per year from 1995 to 1997 in the United States.[351] If the pediatric population comprises all girls age 16 and under, then we estimate that there were a total of 196,520 pregnancies per year from 1995 to 1997.[352] Even if the pediatric population encompasses only girls age 15 and under, we estimate that there were

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[346] *See* Mifeprex Approval Memo at 6.

[347] FDA noted that, for purposes of the *Pediatric Rule*, it would rely "in part, on CDER's current administrative definition of a 'Priority' drug, applied to pediatric populations" to define "meaningful therapeutic benefit." The phrase, "meaningful therapeutic benefit," appears identical in the Subpart H and Priority review contexts. As noted above, Mifeprex was accorded priority review. The modifications to "meaningful therapeutic benefit" for purposes of the *Pediatric Rule* appear to have broadened the scope of the phrase. *See Pediatric Rule*, 63 Fed. Reg. at 66646.

[348] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647.

[349] *Pediatric Rule*, 63 Fed. Reg. at 66634 ("C. Age Groups"). After noting comments to the proposed rule that argued for flexibility in setting age definitions (including a comment arguing for "pediatric patient" to include those "from 0 to 21 years"), FDA stated that "the age ranges identified in the proposal may be inappropriate in some instances" and that it had "deleted the references in the rule to specific age ranges." *Id.* at 66651.

[350] Although FDA acknowledged that the safety and effectiveness of Mifeprex were not studied in girls under age 18 and required a statement to that effect in the labeling, the agency anticipated and even encouraged use in this population when it stated that: "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients." Mifeprex Approval Memo at 7.

[351] *See infra* Appendix B at B-3.

[352] *See infra* Appendix B at B-4.

85,960 pregnancies per year from 1995 to 1997 in this age range.[353] Thus, under any definition of the pediatric population, the 50,000 patient cut-off set forth in the *Pediatric Adopting Release* is exceeded. In sum, *neither* of the requisite conditions for a waiver of the *Pediatric Rule* under the first waiver track provided in Section 314.55 is satisfied.[354]

Second, FDA may also waive the pediatric study requirements if the "necessary studies are impossible or highly impractical because, *e.g.*, the number of such patients is so small or geographically dispersed."[355] FDA explained that "that this ground for waiver [must] be interpreted narrowly":[356]

> Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. . . . Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.[357]

Pediatric Mifeprex studies would not have been either "impossible or highly impractical." As described above and in Appendix B, the population of pediatric females that becomes pregnant each year is large and the female population is evenly distributed throughout the United States. Thus, this second waiver track available under Section 314.55 could not have been satisfied (and FDA apparently has not taken a position to the contrary).

FDA may waive the pediatric study requirement under Section 314.55's third waiver track when "[t]here is evidence strongly suggesting that the drug product would be ineffective or

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[353] *See infra* Appendix B at B-4.

[354] *See* 21 C.F.R. § 314.55(c)(2)(i).

[355] *See* 21 C.F.R. § 314.55(c)(2)(ii).

[356] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

unsafe in all pediatric age groups."[358] As noted above, FDA endorsed the proposition that "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen."[359] Thus, by suggesting that Mifeprex could be used appropriately in the pediatric population, FDA eliminated this third track as a possible basis for waiver.

Absent a waiver or deferral, the *Pediatric Rule* requires any drug application to "contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations . . . ."[360] FDA is authorized instead to extrapolate such data from adult studies "[w]here the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients."[361] The underlying adult studies, however, must be "adequate and well-controlled."[362] As noted above, the Population Council did not provide evidence from adequate and well-controlled studies as to the safety and effectiveness of Mifeprex in the *adult* population. Reliance on these flawed adult studies for a determination of the safety and effectiveness of Mifeprex in the pediatric population was inappropriate. Furthermore, to assume that the effects of a potent antiprogesterone, mifepristone, and a

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[357] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

[358] 21 C.F.R. § 314.55(c)(2)(iii).

[359] Mifeprex Approval Memo at 7.

[360] 21 C.F.R. § 314.55(a). FDA stated that it was waiving the *Pediatric Rule*. Mifeprex Approval Letter at 3. The agency did not assert that it had made a determination that pediatric studies were not required because the adult trials were sufficient to support extrapolation of conclusions as to safety and effectiveness in the pediatric population. However, because FDA failed to provide any justification for its waiver, it is difficult to determine whether the agency was, in fact, relying on this provision to eliminate the pediatric study requirement for Mifeprex.

[361] *See* 21 C.F.R. § 314.55(a).

[362] *See* 21 C.F.R. § 314.55(a).

powerful prostaglandin analogue, misoprostol, in pregnant adults can be extrapolated to pregnant adolescents, who are still developing physiologically and anatomically, is medically unsound.[363]

FDA violated its own rules when it waived the Pediatric Rule in the face of explicit criteria that necessitated compliance with the rule.[364] Furthermore, FDA offered no explanation for its determination to waive the rule. As FDA's treatment of other drugs illustrates, a waiver would have been appropriate only if Mifeprex had already been tested in children and labeled accordingly, or if the *Pediatric Rule's* criteria for waiver were satisfied.[365] Because FDA waived the study requirement in the face of explicit criteria that appear to prohibit such action in this instance, the agency violated its rule. In addition to violating Section 314.55, FDA's unexplained waiver of the *Pediatric Rule* for the Mifeprex NDA constitutes agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.[366]

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[363] The Mifeprex Regimen acts upon the reproductive system, which changes dramatically during adolescence. Adolescents, for example, could face disruptions in ovulatory function as a result of concentrations of mifepristone in developing ovarian follicles, or other health problems. Moreover, teenagers may face heightened risks arising from decreased compliance with the full regimen, poor recall of their last menstrual period, and their reluctance to tell others about their pregnancies.

[364] Of course, a partial waiver of the study requirement is appropriate for the non-adolescent pediatric sub-groups. *See* 21 C.F.R. § 314.55(c)(3). According to *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses*, the pediatric sub-populations other than "adolescents" are: 1) preterm newborn infants; 2) term newborn infants (0 to 27 days); 3) infants and toddlers (28 days to 23 months); 4) children (2 to 11 years). *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 9 (§ 2.5).

[365] In April 2000, FDA approved a suitability petition for Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials, and 9 mg/mL, 10 mL vials, the listed drug products for which are Aredia (Pamidronate Disodium for Injection), 30 mg/vial and 90 mg/vial, and determined that the "proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement . . . is appropriate." *See* Letter, FDA to Mitchall G. Clark (April 18, 2000): at 1 (Docket No. 00P-0091/CPI) (concluding "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed product in the pediatric population since the necessary studies are impossible or highly impractical because the number of patients is small and geographically dispersed"). *See also* Letter, FDA to The Weinberg Group, Inc. (June 13, 2000): at 1-2 (Docket No. 99P-5447/CPI) (approving a generic manufacturer's petition to file an Abbreviated New Drug Application for Cefaclor Chewable Tablets, 125 mg, 187 mg, 250 mg, and 375 mg, the listed drug products for which are Ceclor (Cefaclor) for Oral Suspension, 125 mg/5mL, 187 mg/5mL, 250 mg/5mL, and 375 mg/5mL because FDA determined that the "proposed change in dosage form is subject to the Pediatric Rule" but "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population, because the specific drug products that you reference are adequately labeled for pediatric use").

[366] FDA has required numerous drug sponsors to comply with the *Pediatric Rule*, but it approved Mifeprex without stating its basis for waiving the requirement. *See, e.g.*, Letter, FDA to King & Spalding (June 13, 2000): at 1

K. FDA'S UNEXPLAINED REDUCTION OF THE SPONSOR'S PHASE IV REQUIREMENTS WAS ARBITARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

Not only did FDA improperly and without explanation waive its own pediatric testing requirements, but it also inexplicably narrowed the scope of the Population Council's commitments to conduct post-approval Phase IV studies. As a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects.[367] Phase IV, which occurs after a drug is approved, provides the opportunity to "monitor[ ] the safety of the new drug under actual conditions of use in large numbers of patients."[368] Not only

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(Docket No. 99P-2776/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Oxycodone Hydrochloride and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL, the listed drug product for which is Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg, based on the fact that FDA "has determined that your proposed change in dosage form is subject to the Pediatric Rule and has concluded that investigations are necessary to demonstrate the safety and effectiveness in the pediatric population . . . . Therefore, the Agency concludes that the proposed product should be evaluated for safety and efficacy in the pediatric population."); Letter, FDA to Abbott Laboratories (Sept. 29, 1999): at 1-2 (Docket No. 98P-0821/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Hydromorphone Hydrochloride Injection, 0.2 mg/mL, 30 mL vials, the listed drug product for which is Dilaudid-HP Injection, 10 mg/mL, 5 mL ampoules and 50 mL vials, because the "proposed change in route of administration is subject to the Pediatric Rule," "clinical trials are required for this specific drug product," and "investigations are necessary to demonstrate the safety and effectiveness in the pediatric population").

[367] A.G. Gilman, T.W. Rall, A.S. Nies, P. Taylor, eds., *The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990): at 77 ("Although assessment of risk is a major objective of [clinical trials], this is far more difficult than is the determination of whether a drug is efficacious for a selected condition. Usually about 500 to 300 carefully selected patients receive a new drug during phase-3 clinical trials . . . . Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly.").

[368] Bertram G. Katzung, M.D., ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk, CT: Appleton & Lange, 1989): at 56. "Final release of a drug for general prescription use should be accompanied by a vigilant postmarketing surveillance program. The importance of careful and complete reporting of toxicity after marketing approval by the FDA can be appreciated by noting that many drug-induced effects have an incidence of 1:10,000 or less. . . . Because of the small numbers of subjects in phases 1-3, such low-incidence drug effects will not generally be detected before Phase 4, no matter how carefully the studies are executed. Phase 4 has no fixed duration." *Id.* at 56-7.

did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the Phase IV trials that it would perform.

In response to an FDA request, on September 16, 1996, the Population Council agreed to conduct a set of Phase IV studies.[369] FDA "reminded" the Population Council of these commitments in both the 1996 and 2000 Approvable Letters.[370] The Population Council agreed to perform studies with the following objectives:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect on children born after treatment failure.[371]

These studies would have addressed some of the health issues that were not evaluated during pre-approval testing.

The Mifeprex Approval Letter released on September 28, 2000, however, contains only two Phase 4 study obligations, a radical curtailment of the earlier commitments.[372] The letter

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[369] FDA made its request on August 22, 1996, after it had received Phase IV study recommendations from the FDA Advisory Committee. *See* Medical Officer's Review, *infra* Appendix A, at 20-24.

[370] *See* 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[371] 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[372] *See* Mifeprex Approval Letter, *infra* Appendix A, at 2-3.

stated that "the following Phase 4 commitments, specified in [the Population Council's] submission dated September 15, 2000 . . . *replace all previous commitments* . . . ."[373]

(1) "A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[374]
(2) "A surveillance study on outcomes of ongoing pregnancies."[375]

FDA stated that "[p]revious study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms."[376] The agency, thus, compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate Phase IV study.[377] The Approval Letter explained that

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[373] Mifeprex Approval Letter, *infra* Appendix A, at 2.

[374] Mifeprex Approval Letter, *infra* Appendix A, at 3. The Population Council acknowledged three weaknesses of this study. First, the sample size would be limited so that the sponsor "will only be able to determine whether the combined safety rates of hospitalizations, medically necessary surgical interventions, and IV fluids in each of the two cohorts are within plus or minus 5 percentage points of the expected 2% rate. We will not be able to detect differences of individual safety outcomes such as blood transfusions and deaths." *See* Amendment 062 to the NDA, Revised Materials (Sept. 19, 2000): at 3. [FDA FOIA Release: MIF 007896-7903]. Second, the Population Council predicted that it might have difficulty finding women who were referred to another provider for care. *Id.* at 3-4. Third, it might be difficult to find women who did not return for their follow-up visit. *Id.* at 4. These three study weaknesses appear, at least in part, to stem from faulty selection criteria for study subjects. Patients should not be enrolled in a study unless they are willing to comply with follow-up visits and telephone inquiries. Additionally, informed consent forms authorize investigators to request medical records from other health care providers.

[375] Mifeprex Approval Letter, *infra* Appendix A, at 3.

[376] Mifeprex Approval Letter, *infra* Appendix A, at 3. These issues were characterized by the sponsor as "Secondary Study Objectives." *See* Amendment 062 to the NDA (Sept. 19, 2000): at 1. The failure to consider each issue in a separate study is likely to compromise the quality of the data generated. Because the study is primarily focused on a provider-level variable (ability to provide surgical intervention), the study will not necessarily yield a meaningful sample size for each of the relevant patient-level variables (age and smoking status). Patients will be enrolled "consecutively from each provider until the provider's quota is met." *See id.* at 2.

[377] The Population Council submitted data from the Spitz Study on 106 women age 35 and older and 51 patients under age 20. *See* Mifeprex Approval Letter, *infra* Appendix A, at 7. However, the effects and potential age-specific risks of the Mifeprex Regimen on women outside the tested age range deserve separate consideration in studies with far more subjects. Approximately 279,000 girls nineteen and younger and more than 84,000 women over the age of 35 obtain abortions in the United States annually. *See* Appendix B, *infra*, at B-4 (§§ 5 and 6). The Mifeprex Regimen, which directly interacts with the reproductive system, could conceivably interfere with pubertal development, as discussed above, and might pose unique risks to women who are nearing the end of their reproductive years.

"the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996."[378]

It appears, however, that the modifications came largely in response to the Population Council's unwillingness to explore the ramifications of the Mifeprex Regimen. On August 18, 1999, the Population Council acknowledged its Phase IV commitments, but stated that "[w]e plan to discuss in more detail and develop a consensus with the FDA post-NDA approval."[379] The Population Council complained, for example, that "[a] prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades."[380] Similarly, the Population Council informed FDA that it was "not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing

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[378] Mifeprex Approval Memo, *infra* Appendix A, at 7. FDA's conclusion that the reduction to only two Phase IV studies "reflect[s] current postmarketing questions" ignores a number of issues about Mifeprex that remain unexplored. Because mifepristone interferes with pregnancy by binding to the progesterone receptor in the placenta, there is concern that the drug may affect not only the uterus, but the brain, breasts, adrenal glands, ovaries, and immune cells, all of which also have progesterone receptors. Concerns that mifepristone may have a carcinogenic effect on breast tissue have also been expressed. *See, e.g.,* Testimony of Dr. Joel Brind, FDA Hearings Transcript, *infra* Appendix A, at 172-175. Mifepristone also could affect the pituitary gland, the adrenal glands, and immune cells, all of which have glucocorticoid receptors. In addition, it is unclear whether a woman who undergoes multiple mifepristone-misoprostol abortions could suffer adverse effects. *See* ACOG Practice Bulletin, *infra* Appendix A, at 9 ("No well-designed prospective studies address the issue of repeat medical abortion."). Questions also remain about possible effects on the children born to women who have terminated a previous pregnancy with the Mifeprex Regimen. *See, e.g.,* P. Van der Schoot and R. Baumgarten, "Effects of Treatment of Male and Female Rats in Infancy with Mifepristone on Reproductive Function in Adulthood," *Journal of Reproduction and Fertility* 90 (1990): 255-66 (finding that rats exposed to mifepristone in their infancy suffered infertility in adulthood)[FDA FOIA Release: MIF 007165- 007176].

[379] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999).

[380] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999); *see also* Mifeprex Approval Memo at 7 (agreeing with the Population Council's reasoning).

this, as it could violate women's privacy."[381] The Population Council's concerns about privacy lack merit. Patients who participate in clinical trials give their consent to participate and to be monitored, thus eliminating concerns about privacy. Similarly, FDA should not have accorded undue weight to the Population Council's protestations about the potential expense of the trials; drug sponsors, who stand to profit from a drug's sales, are responsible for bearing the expenses incurred in establishing the safety and efficacy of a drug.[382]

FDA's acquiescence in the Population Council's reduction in its Phase IV commitments compounded the Agency's earlier failure to require the sponsor to conduct clinical trials in accordance with the requirements of Section 314.126 of FDA's rules. FDA's inadequately justified curtailment of the sponsor's Phase IV study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

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[381] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999). The necessity of long-term monitoring is particularly critical to compensate for the unusually short tracking periods employed in the U.S. Clinical Trial, in which investigators generally did not track patients after their third visit. *See* Spitz Article, *infra* Appendix A, at 1242. "Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted." *Id.* Five percent of the participants in the U.S. Clinical Trial were not tracked through the third visit (which would have occurred on Day 15) because they failed to return for it, suggesting that each of these women was last seen on Day 3, only 2 days after the initial administration of mifepristone. *See* Medical Officer's Review, *infra* Appendix A, at 10. Abbreviated follow-up periods run counter to ICH standards, which state that in clinical trials of drugs intended for use during pregnancy, "followup of the pregnancy, fetus, and child is very important." *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.1.4.3) ("Special populations").

[382] In fact, the sponsors of Mifeprex received substantial outside funding to support their efforts. *See* "Mifepristone: FDA Approval Imminent, Advocates Predict," *Kaiser Daily Reproductive Health Report* (Sept. 28, 2000) (available at: <http://www.kaisernetwork.org/reports/2000/09/kr000928.3.htm>) ("Danco Laboratories, LLC, a small New York-based company, will market the drug with funding from billionaire financier Warren Buffet and hedge-fund czar George Soros and a $10 million loan from the David and Lucile Packard Foundation."); Sharon Bernstein, "Persistence Brought Abortion Pill to U.S.," *Los Angeles Times* (Nov. 5, 2000): at A1 ("The Population Council raised $16 million from like-minded foundations, including the Open Society Institute of New York, which is the philanthropic arm of billionaire George Soros, and the California-based Kaiser Family Foundation.").

IV. PETITIONERS SEEK LEAVE TO AMEND

The Petitioners respectfully inform FDA that they may file amendments to this Petition as information becomes available from Freedom of Information Act requests made before the filing date of this document.[383]

V. CONCLUSION

For the foregoing reasons, the Petitioners respectfully request that the Commissioner immediately enter an administrative stay to halt any further distribution and marketing of Mifeprex until final agency action is taken on this Petition. The Petitioners also respectfully request that the Commissioner revoke approval of Mifeprex for the medical termination of pregnancies less than 49 days' gestation. On the basis of the evidence presented above, the Petitioners respectfully request a full FDA audit of the French and U.S. Clinical Trials.[384]

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[383] The Petitioners have filed numerous Freedom of Information Act ("FOIA") requests with FDA that remain unanswered, including: 1) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of FDA's letter to the Population Council dated, or mailed, on or about June 1, 2000, along with any attachments, appendices, and other accompanying materials"); 2) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of the new drug application . . . filed . . . on or about March 18, 1996 (NDA 20-687)"); 3) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001) (seeking a copy of data submitted by the sponsor "related to the use of mifepristone by women over the age of thirty-five, females under the age of eighteen, and women who smoke" and of the Phase IV study protocols submitted by the Sponsor and any Phase IV trial data); and, 4) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Feb. 6, 2002) (seeking a correct listing of all drug applications approved pursuant to 21 C.F.R. § 314.520 and documents detailing FDA's reasoning for approving drugs under this section of its rules).

[384] An audit of the U.S. Clinical Trial is additionally warranted because of an unusual data management decision made by the Population Council with the apparent approval of the FDA:

> Thank you for speaking with me the other day about our data dilemma. In response to our conversation, we have decided to create two versions of our electronic database from the mifepristone study. The first will reflect exactly the physical copies of the patient record forms, and will be used as the basis for our regulatory submissions to you. The second version will closely match the first, particularly on safety and efficacy indicators, but certain variables will be modified to create an internally consistent database that we can use easily for our planned scholarly publications on the topic. We will keep careful track of the changes we make and we will be able to explain them to an FDA auditor should the need arise. One result

VI. ENVIRONMENTAL IMPACT

This Petition for withdrawal of approval of an NDA is categorically excluded under 21 C.F.R. § 25.31(d). An environmental impact statement is, thus, not required.

VII. ECONOMIC IMPACT

The Economic Impact information shall be submitted only when and if requested by the Commissioner following review of the Petition, in accordance with 21 C.F.R. § 10.30.

CERTIFICATIONS AND SIGNATURES

On behalf of the petitioner organizations listed below, we the undersigned hereby certify that, to the best of petitioners' knowledge, this Citizen Petition is true and accurate. It includes all available information relevant to this Petition, including information both favorable and unfavorable to Petitioners' position in this matter.

So executed this 15 day of August 2002.

Donna Harrison MD

Donna Harrison, M.D.
Chairperson, Subcommittee on Mifeprex
American Association of Pro-Life
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of this approach to handling the data is that certain aspects of our future publications may differ from tabulations that appear in our regulatory submissions.

Letter, Charlotte Ellertson, Population Council, to [Redacted], FDA/CDER (July 28, 1997): at 1 [FDA FOIA Release: MIF 006489].

So executed this 13 day of August 2002.

Gene Rudd, M.D.
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So executed this 20th day of August 2002.

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Table of Contents

Citizen Petition (Mifeprex) Documents

Description of Article/Document	TAB
Exhibit A: Selected Bibliography.	A
Exhibit B: Statistics Used in the Petition.	B
Exhibit C: FDA's Subpart H Webpage (Chart).	C
Exhibit D: Printouts from Mifeprex abortion websites illustrating deviations from the approved regimen.	D
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Citizen Petition (Mifeprex) Documents

Description of Article/Document	TAB
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