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VIA HAND DELIVERY

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**Re: Docket No. 02P-0377
Response to Opposition Comments filed by The Population Council, Inc. and
Danco Laboratories, LLC**

We submit these comments on behalf of The American Association of Pro Life Obstetricians and Gynecologists (“AAPLOG”), the Christian Medical Association (“CMA”), and Concerned Women for America (“CWA”) (collectively, “the Petitioners”), in response to Opposition Comments filed by the makers/distributors of Mifeprex™ (mifepristone) 200 mg tablets (NDA 20-687).¹ In particular, The Population Council, Inc. (“the Council”) and Danco Laboratories, LLC (“Danco”) (collectively, “the Sponsor”) submitted comments on March 13, 2003 opposing the Citizen Petition and Request for Administrative Stay (“Petition”) filed by the Petitioners on August 20, 2002.²

Not surprisingly, the Council and Danco ask the Food and Drug Administration (“FDA”) to maintain the status quo, so that they can continue to sell Mifeprex, a “non-surgical” alternative to abortion. By contrast, the Petitioners seek to protect women from the unknowing use of a dangerously unsafe drug by pursuing an immediate stay and withdrawal of FDA’s approval of the new drug application (“NDA”) for mifepristone.

Although opposing comments were inevitable, the Petitioners are concerned that the Sponsor has refused to acknowledge any problems regarding the safety, effectiveness and overall

¹ Opposition of The Population Council, Inc. and Danco Laboratories, LLC to Citizen Petition and Request for Administrative Stay Regarding Mifeprex® (Mifepristone), Docket No. 02P-0377 (March 13, 2003) (“Opposition Comments”) (available at: <<http://www.fda.gov/ohrms/dockets/dailys/03/Mar03/031303/031303.htm>>).

² Citizen Petition of the American Association of Pro Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America, Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days’ Gestation, Docket No. 02P-0377 (filed Aug. 20, 2002) (available at: <<http://www.aaplog.org/newscitizenpetitionru486.htm>>).

medical suitability of the Mifeprex Regimen.³ The Petitioners are not surprised, however, that the Sponsor has failed to produce medical-scientific data and adequate explanations for the administrative irregularities described in the Petition. This failure is consistent with the Petitioners' contention that the clinical data in support of the Mifeprex Regimen are scarce, not the product of adequate and well-controlled trials, and cannot support a reasoned risk-benefit analysis by FDA. Instead, the available evidence points to the fact that Mifeprex should never have been approved by FDA.

We have set forth below our responses to the Sponsor's Opposition Comments, along with additional evidence that the safety and effectiveness of Mifeprex have not been established in accordance with FDA's regulations. In particular, the drug, which was not lawfully entitled to consideration under Subpart H, could not have been approved apart from that provision's special distribution restrictions; the clinical trials relied on to support the NDA were legally and clinically insufficient; the inclusion of misoprostol in the Mifeprex Regimen without a corresponding misoprostol approval was unlawful; and the Regimen's use is inherently unsafe, as proven by recent life-threatening adverse events and even deaths. With this evidence, FDA is both statutorily empowered and obligated to grant an Administrative Stay to suspend the Mifeprex NDA approval and expedite withdrawal proceedings.

I. The Safety and Effectiveness of Mifeprex Have Not Been Established in Accordance with FDA's Regulations.

FDA's approval of a drug product must rest on the Agency's conclusion that the drug is safe and effective for its labeled conditions for use. In the case of Mifeprex, the Petitioners previously provided evidence that the NDA should not have been approved, and the Sponsor's Opposition Comments did not rebut that evidence. In fact, as described below, although the Opposition Comments reiterate the Sponsor's confidence in the safety and efficacy of the Mifeprex Regimen, they also expose the dearth of pre- or post-approval evidence for that position. Consequently, given the body of evidence now before FDA, the Agency should withdraw its approval of the Mifeprex NDA at this time.

A. Subpart H Enables FDA to Place Special Restrictions on Especially Risky Drugs like Mifeprex.

Although Petitioners maintain their original position that FDA's reliance on Subpart H was unlawful for this drug, the Sponsor's response that Mifeprex could have been approved alternatively under Section 505 is incorrect. The Sponsor's Opposition Comments repeat an argument that the Sponsor made when it was trying to convince FDA not to use Subpart H – that “[t]he restrictions FDA imposed under Subpart H could as well have been imposed (and enforced) under Section 505 [of the FD&C Act]⁴ itself, without reference to Subpart H.”⁵ The

³ When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Response, “Mifeprex Regimen” will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

⁴ 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.*).

fact that FDA proceeded under Subpart H suggests that the Agency did not subscribe to this argument. Indeed, had FDA taken this position, it would not have promulgated the restricted distribution prong of Subpart H,⁶ but would simply have relied on Section 505 to impose restrictions. When FDA adopted Subpart H, it noted that “the restrictions to ensure safe use contemplated for approvals under [Subpart H] are authorized by statute.”⁷ FDA went on to explain that Subpart H would enable the Agency to impose on drugs restrictions “necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use.”⁸ Additional restrictions are necessary because Mifeprex and other Subpart H drugs carry greater risks than drugs approved through the typical new drug approval processes.⁹ In short, when FDA adopted Subpart H, it added a new tool to its regulatory toolbox enabling it to approve drugs that otherwise could not have been approved because the safe usage mandates in Section 505 would not have been satisfied.¹⁰ Therefore, the Sponsor errs in asserting that the approval of the Mifeprex NDA is independently grounded in Section 505(d).

The Sponsor also claimed that its cooperation with FDA to devise restrictions obviates the need to rely on Subpart H.¹¹ The Sponsor’s unflinching confidence in the safety of mifepristone even in the face of scientific evidence to the contrary is part of the reason that restrictions under section 505 could not be effective. The Sponsor’s bias in favor of Mifeprex clouds its analysis of the inherent hazards of the Regimen. In fact, the Sponsor refused to participate in devising restrictions that were designed to protect Mifeprex patients.

As “evidence” of its cooperation, the Sponsor pointed to the restricted distribution plan it proposed to an FDA advisory committee in 1996.¹² The FDA Advisory Committee’s reaction to

⁵ See Opposition Comments at 3 (citing 21 U.S.C. § 355). See also Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 3-5 [FDA FOIA Release: MIF 001333-49].

⁶ 21 C.F.R. § 314.520.

⁷ New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942, 58951, § 20 (Dec. 11, 1992) (“*Subpart H Final Rule*”).

⁸ *Subpart H Final Rule*, 57 Fed. Reg. at 58951, § 20. See also New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234, 13237, sec. III.B.3. (April 15, 1992) (“*Subpart H Proposed Rule*”) (noting that without Subpart H restrictions, 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”).

⁹ See *Subpart H Final Rule*, 57 Fed. Reg. at 58952, § 23 (“The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction.”).

¹⁰ FDA explained 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.” *Subpart H Final Rule*, 57 Fed. Reg. at 58951-52, § 20.

¹¹ See Opposition Comments at 5-6.

¹² See Opposition Comments at 4. The Sponsor was referring to a plan presented to FDA’s Reproductive Health Drugs Advisory Committee (“FDA Advisory Committee”). See FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 7 (July 19, 1996) (*FDA Hearings Transcript*) [FDA FOIA Release: MIF 005200-90, MIF 005209]. The Petitioners will, at times, cite to documents

the proposal, however, reveals its inadequacy; the Advisory Committee stated that “[w]e agree in concept with the proposal but have serious reservations on how it is currently described in terms of assuring safe and adequate credentialing of providers.”¹³ The Sponsor also cited to its “comprehensive distribution plan” submitted in January 2000 and to its revised distribution plan submitted to FDA in March 2000.¹⁴ The Sponsor indicated in its January 2000 submission that it was providing the proposal only “in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns,”¹⁵ and the March 2000 submission was prefaced with a denial that mifepristone was “a highly toxic and risky drug.”¹⁶ However, as the Petition explained, the plans that the Sponsor submitted on both occasions were not designed with the safety of the patient in mind and when FDA proposed a set of restrictions that focused on patient safety, the Sponsor balked.¹⁷ Further, even if the Sponsor had participated willingly in drawing up restrictions that embodied key safeguards for patients, FDA could not necessarily expect similar cooperation from future generic producers of mifepristone.¹⁸

Conclusion

As explained above, the Mifeprex approval cannot rest independently on Section 505(d) of the FD&C Act. The Sponsor refused to acknowledge that there are serious risks associated with the Mifeprex Regimen, let alone to propose restrictions designed to counteract those risks. FDA approved Mifeprex under Subpart H in order to impose mandatory safety restrictions on the distribution and use of the drug. That being said, the proper course would have been for FDA to have rejected the NDA because Mifeprex is unsafe and ineffective under Section 505 and fails to satisfy the Subpart H prerequisites that it treat a serious or life-threatening illness and provide a meaningful therapeutic benefit above existing treatments.¹⁹

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 (“FOIA”) 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 of the document cited, 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>>.

¹³ FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45, MIF 000545] (citing statement voted on unanimously by the FDA Advisory Committee).

¹⁴ See Opposition Comments at 4-5.

¹⁵ Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26, MIF 000525]. The Sponsor’s reference to the “unique situation surrounding abortion provision in the United States” reveals the Sponsor’s primary concern in proposing restrictions, namely that the safety and confidentiality of *abortion providers* be maintained, not that patient safety be maximized.

¹⁶ Responses by Population Council to “FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)” (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24, MIF 000523].

¹⁷ See Section I.D. herein; see also Petition at 50-54.

¹⁸ See FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85, MIF 000585] (“Subpart H approval will also allow the FDA to impose similar distribution restrictions and system on any future generic mifepristone approved for this indication.”).

¹⁹ See Petition at 18-23 (explaining why Mifeprex was an inappropriate candidate for Subpart H).

B. The Mifeprex Clinical Trials Were Legally and Clinically Insufficient.

The Petition describes numerous problems that plagued the clinical trials underlying the approval of Mifeprex. The Sponsor's Opposition Comments, rather than demonstrating the sufficiency of the clinical trial data that formed the basis for the Mifeprex NDA, heightened the Petitioners' concerns about the legal and clinical sufficiency of the French and U.S. Clinical Trials (collectively, "Mifeprex Trials"). First, a close reading of the Sponsor's Opposition Comments reveals that the Mifeprex Trials were not historically controlled but, rather, were *uncontrolled*.²⁰ Second, even if the Mifeprex trials were historically controlled, as the Sponsor maintains, the use of historically controlled trials to support this NDA violated clearly established FDA rules and agency policies.²¹ Finally, the Sponsor's additional arguments in support of the scientific adequacy of the Mifeprex trials do not answer the objections presented in the Petition. Untested by adequate clinical trials, the Mifeprex Regimen cannot be deemed to be safe and effective; accordingly, the marketing of Mifeprex must be halted.

1. The Mifeprex Trials Were Uncontrolled.

A review of the record regarding the scope and methodology of the trials, prompted by the Sponsor's defense of the Mifeprex Trials,²² reveals that the trials used to support the Mifeprex NDA were not historically controlled, but were *uncontrolled*.²³ The Petition cited to the discussion between a member of FDA's Advisory Committee and an FDA official in which the Mifeprex Trials were characterized as "historically" controlled.²⁴ The Petitioners noted, however, that the Mifeprex Trials appeared to have been uncontrolled.²⁵

The French Clinical Trials consisted of two studies in which all participants were given a mifepristone-misoprostol regimen, and no concurrent control group underwent a different abortion treatment.²⁶ The Sponsor did not describe any historical (or "external") control group,²⁷

²⁰ Because the Mifeprex Regimen was the first drug regimen that FDA approved to induce abortions, in order to scientifically demonstrate the safety and effectiveness of this drug regimen, the Sponsor should have compared this new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period.

²¹ The Petitioners believe that a longitudinal analysis of all past occasions on which FDA accepted uncontrolled and historically controlled trials as an adequate basis for an NDA and all past occasions on which it has rejected the use of uncontrolled or historically controlled clinical trials would demonstrate the inadequacy of the clinical trials underlying this NDA. FDA is uniquely qualified to perform such an analysis.

²² See Opposition Comments at 6-9.

²³ One consequence of the failure to conduct properly controlled trials is that a *statistical* evaluation of effectiveness could not be made. As FDA's statistical reviewer noted, with reference to the French trials: "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy." See FDA, Statistical Review and Evaluation (May 21, 1996): at 7-8.

²⁴ Petition at 36, n.168 (referring to statements by Dr. Cassandra Henderson, a member of the FDA Advisory Committee, and FDA's Dr. Ridgely C. Bennett at the Advisory Committee Hearings).

²⁵ Petition at 35.

²⁶ Letter, C. Wayne Bardin, Population Council, to FDA/CDER (June 5, 1995) (Submission Serial Number: 131) at 3-4 ("Bardin Letter") [FDA FOIA Release: MIF 004746-47]. The patients in the French Clinical Trials took 600 mg of mifepristone followed by 400 µg of misoprostol. In one of the French Clinical Trials, some patients received an

nor did the Sponsor indicate that any of the well-established scientific guidelines for selecting a proper control group before commencing a historically controlled study were used for the French Clinical Trials.²⁸ The Sponsor, nevertheless, informed FDA that “[a]ll studies conducted with mifepristone in the induction of abortion can be regarded as having historical controls which consist of the body of information available on abortion using surgical procedures.”²⁹ This observation appears to be the only basis for the Sponsor’s claim that the French Clinical Trials were historically controlled, and it is inadequate.

The U.S. Clinical Trial mimicked the design of the French Clinical Trials.³⁰ All participants were given a mifepristone-misoprostol regimen, and no concurrent control group underwent a different abortion treatment. Descriptions of the U.S. Clinical Trial do not mention a control group, historical or otherwise, or the procedures according to which a control group was selected.³¹ The absence of any reference to a control group suggests that the U.S. Clinical Trial was not historically (externally) controlled.³²

The Sponsor’s failure to precisely identify a historical control group is fatal to its claim that the Mifeprex Trials were historically controlled. Postulating the existence of some generic,

extra 200 µg of misoprostol if the first 400 µg was not sufficient to complete the abortion. The approved Mifeprex Regimen consists of 600 mg of mifepristone followed by 400 µg of misoprostol.

²⁷ Bardin Letter at 3-4.

²⁸ FDA guidance lists “some approaches to design and conduct of externally controlled trials could lead them to be more persuasive and potentially less biased:”

A control group should be chosen for which there is detailed information, including, where pertinent, individual patient data regarding demographics, baseline status, concomitant therapy, and course on study. The control patients should be as similar as possible to the population expected to receive the test drug in the study and should have been treated in a similar setting and in a similar manner, except with respect to the study therapy. Study observations should use timing and methodology similar to those used in the control patients. To reduce selection bias, selection of the control group should be made before performing comparative analyses; this may not always be feasible, as outcomes from these control groups may have been published. Any matching on selection criteria or adjustments made to account for population differences should be specified prior to selection of the control and performance of the study.”

FDA, “Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials,” (Rockville, Md.: May 2001): at 27 (§ 2.5.2) (*ICH: E10*). *ICH: E10* is available at: <<http://www.fda.gov/cder/guidance/4155fnl.pdf>>.

²⁹ Bardin Letter at 4.

³⁰ For a description of the U.S. Clinical Trial, see Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri 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].

³¹ See, e.g., Spitz Article.

³² The Spitz Article does compare two groups, patients who are differentiated by the age of their pregnancies, but a comparison of that type does not generate data about whether mifepristone-misoprostol abortions are safe and effective. To the extent the Sponsor believed that a correlation existed between the age of the pregnancy and the safety and efficacy of mifepristone-misoprostol abortions, any historical control group that the Sponsor used should have been classified by, among other characteristics, gestational age.

undefined comparison group based on the literature about surgical abortion does not suffice.³³ In sum, the Mifeprex Trials were uncontrolled and cannot support the Mifeprex NDA.³⁴

2. Mifeprex Is Not a Drug for Which Historically Controlled Trials Were Appropriate.

Assuming *arguendo*, as the Sponsor maintains, that the Mifeprex Trials were historically controlled, they were nevertheless not *adequately* controlled and did not provide an adequate basis for approving the Mifeprex NDA. In its Opposition Comments, the Sponsor erroneously suggested that “historically controlled” trials yield data of the same quality as data generated in concurrently controlled trials.³⁵ In fact, the scientific community (and FDA specifically) regard historically controlled studies to be little better than uncontrolled studies and, therefore, generally disfavor their use with a few well-defined exceptions.³⁶

Mifepristone-misoprostol abortions do not fall within any of those exceptions. The Rochester Glossary states that historical controls are “mainly used in the study of rare diseases” in which sample size would not be sufficient to support a randomized clinical trial.³⁷ This exception is inapplicable because the number of pregnant women seeking to terminate their pregnancies is large enough to support randomized, concurrently controlled trials. Section 314.126(b)(2)(v) of FDA’s rules cautions that the use of historical controls is “usually reserved

³³ In addition, the Sponsor, in its Opposition Comments, invented a historical control group *ex post facto* by comparing the rate of spontaneous abortions in the general population of pregnant women with the rate of abortions in patients who underwent a mifepristone-misoprostol regimen during the Mifeprex Trials. See Opposition Comments at 6-7 (“In these major studies, 92-95% of the 2508 women evaluated for efficacy had complete abortions By comparison, the rate of spontaneous abortion in the first trimester is assumed to be about 10%.”). Using the general population as a historical control group and retrospectively assuming a rate of spontaneous abortion in this group is not a scientifically acceptable approach to identifying a control group, particularly when, as here, an established surgical treatment group could have been used as the control group.

³⁴ Section 314.126(e) of FDA’s rules states that “[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness.” 21 C.F.R. § 314.126. A publicly available FDA staff presentation about clinical trials illustrates this point. The presentation explained, under the heading “Phase 3 – Comparative trial to evaluate drug,” “Comparator group important – Standard of care, placebo, never nothing in serious or life-threatening diseases (ICH E3, E9, E10).” See Peter A. Lachenbruch, “Some Things You Always Wanted to Know about Clinical Trials but Were Afraid to Ask,” Slide Presentation for *CBER 101: An Introduction to the Center for Biologics Evaluation and Research (CBER)* (March 24-26, 2003): at 5 (emphasis in original) (available at: <http://www.fda.gov/cber/summaries/cber101032403pl.pdf>).

³⁵ See Opposition Comments at 6-8.

³⁶ For example, the Research Subjects Review Board of the University of Rochester Medical Center authored a guidance document, which states that “[h]istorical controls are considered to be the least reliable because they compare results obtained in another time, in another place and by another investigator.” University of Rochester Medical Center, Research Subjects Review Board, “Glossary of Research Terms,” at 2 (“Rochester Glossary”) (available at: <http://www.urmc.rochester.edu/rsrb/pdf/glossary.pdf>). Similarly FDA has explained, “[t]he limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, etc.) and deserve particular attention.” FDA/CDER, *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988): at 54.

³⁷ Rochester Glossary at 2 (“Historical controls are mainly used in the study of rare diseases where the **n** is not sufficient for a randomized clinical trial.”).

for special circumstances” and cites “studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).”³⁸ Mifepristone-misoprostol abortions do not fit within either of these categories. First, the Regimen does not treat a condition with “high and predictable mortality.” Second, the effects of the Regimen are not “self-evident” as in the case of general anesthetics. The Sponsor’s discussion of the adequacy of its trial data reflects the Sponsor’s fundamental misconception that there are only two possible outcomes of the Mifeprex Regimen, both of which are self-evident: regimen failure (failed abortion) and regimen success (death and complete expulsion of the fetus). The Sponsor’s focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes. Such outcomes include tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects.

The Sponsor’s reliance on FDA Guidance, *ICH: E10*, is also misplaced.³⁹ Although *ICH: E10* includes a discussion of situations in which externally controlled trials may be used, it also warns of their inherently problematic nature.⁴⁰ The Sponsor’s reliance on the acknowledgement in *ICH: E10* that historical controls are appropriate in some circumstances is misplaced. *ICH: E10* explains:

An externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course. It is often possible, even in these cases, to use alternative, randomized, concurrently controlled designs (see section 2.1.5).⁴¹

³⁸ 21 C.F.R. § 314.126(b)(2)(v) provides:

Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

³⁹ Opposition Comments at 7.

⁴⁰ See *ICH: E10* at 29 (§ 2.5.7) (“The externally controlled study cannot be blinded and is subject to patient, observer, and analyst bias; these are major disadvantages. It is possible to mitigate these problems to a degree, but even the steps suggested in section 2.5.2 cannot resolve such problems fully, as treatment assignment is not randomized and comparability of control and treatment groups at the start of treatment, and comparability of treatment of patients during the trial, cannot be ensured or well assessed. It is well documented that externally controlled trials tend to overestimate efficacy of test therapies. It should be recognized that tests of statistical significance carried out in such studies are less reliable than in randomized trials.”). See also Henry Sacks, Ph.D., M.D., Thomas C. Chalmers, M.D., Harry Smith, Jr., Ph.D., “Randomized Versus Historical Controls for Clinical Trials,” *The American Journal of Medicine* 72 (Feb. 1982): 233-240, 233 (“The data suggest that biases in patient selection may irretrievably weight the outcome of [historical controls] in favor of new therapies.”).

⁴¹ *ICH: E10* at 28 (§ 2.5.4).

Even proponents of mifepristone-misoprostol abortions would not argue that such abortions are superior to alternative methods of abortion.⁴² In fact, the Mifeprex Regimen has been shown to be an inferior method of abortion.⁴³ Absent a clear belief in the Regimen's superiority, concurrently controlled trials should have been performed.⁴⁴ Furthermore, pregnancies often do not follow a "well-documented, highly predictable course."⁴⁵ Mifepristone-misoprostol abortions do not satisfy either prong of the *ICH: E10* prerequisite for the use of historically controlled studies.⁴⁶

3. The Mifeprex Clinical Trials Did Not Establish a "Meaningful and Therapeutic Benefit" As Required By Subpart H.

Drugs, like Mifeprex, approved pursuant to Section 314.520 (Subpart H) of the Agency's rules,⁴⁷ must provide a "meaningful therapeutic benefit to patients over existing treatments."⁴⁸ Subpart H drugs "will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."⁴⁹ The Sponsor argued that "meaningful therapeutic benefit" does not impose design features for the clinical trials required to support an NDA approved pursuant to Subpart H.⁵⁰ The Sponsor's position is inconsistent with the plain meaning of the rule. Subpart H is reserved for drugs that have a higher risk profile than drugs approved through standard FDA processes. A meaningful therapeutic benefit over available therapies justifies the heightened risks, and only well-controlled clinical trials can demonstrate that such a benefit exists.⁵¹

⁴² See, e.g., Richard Hausknecht, M.D., "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003): 463-65, 465 ("Hausknecht Article") ("Which approach to early abortion, medical or surgical, is safer remains unknown but it does appear that medical abortion is as safe as early surgical abortion. There are no recent data on failed surgical abortions but the failure rate of mifepristone/misoprostol medical abortions is higher than that reported decades ago for suction curettage.")

⁴³ Petition at 21-22 (discussing 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 [FDA FOIA Release: MIF 000438-44]).

⁴⁴ The Petitioners believe that trials comparing mifepristone-misoprostol abortion with the surgical alternative were not conducted for precisely this reason (*i.e.*, such trials would have demonstrated that mifepristone-misoprostol abortions were inferior). Because of its inferiority, the Mifeprex Regimen is contraindicated.

⁴⁵ Even though pregnancy occurs regularly, complications arise during pregnancy on a frequent basis (*e.g.*, approximately 2% of pregnancies are ectopic and others involve such complications as high blood pressure, ruptured placenta, infection, cysts, abnormal pain, anemia, and fetal malposition).

⁴⁶ Even if mifepristone-misoprostol abortion were deemed to be an acceptable candidate for historically-controlled testing, the Sponsor should have attempted to devise concurrently controlled trials anyway. *ICH: E10* states that even when historically controlled testing may be appropriate, "[i]t is often possible . . . to use alternative, randomized, concurrently controlled designs." *ICH: E10* at 28 (§ 2.5.4).

⁴⁷ 21 C.F.R. § 314.520.

⁴⁸ 21 C.F.R. § 314.500.

⁴⁹ See *Subpart H Final Rule*, 57 Fed. Reg. at 58953, § 25.

⁵⁰ Opposition Comments at 8.

⁵¹ The Sponsor also argued that by the time FDA decided to approve Mifeprex using Subpart H, the Sponsor had completed the Mifeprex Trials and that FDA could not have required the Sponsor to modify the trial design and perform new trials for Subpart H purposes. See Opposition Comments at 9, n. 4. FDA is under no obligation to

The Sponsor argued that two of the examples of “meaningful therapeutic benefit” listed in Section 314.500 (“ability to treat patients unresponsive to, or intolerant of, available therapy”) present situations in which comparative trials with the existing therapy are not feasible.⁵² Yet, sponsors who intend their drugs to treat unresponsive or intolerant patients are not exempt from the requirement to conduct “well-controlled” trials. In fact, Subpart H trials are routinely designed to compare, in unresponsive or intolerant patients, the safety and effectiveness of the new therapy with either the standard of care or a placebo.⁵³

The Sponsor further claimed that FDA “routinely approves Subpart H drugs on the basis of study designs that do not compare the Subpart H drug directly to existing therapy.”⁵⁴ In support of this claim, the Sponsor offered one example, the Subpart H approval of the leprosy drug, Thalomid (thalidomide).⁵⁵ That example is inapposite because the Thalomid NDA was supported by three controlled trials despite the existence of factors that might have supported an exemption from the standard trial requirements.⁵⁶ In one of the three underlying trials, thalidomide plus the standard treatment was compared against the standard treatment alone plus a placebo.⁵⁷ This study design allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care – in direct contrast to the faulty study designs and minimal statistical analysis associated with the Mifeprex NDA.

Conclusion

By statute and agency regulation, drug applications must be supported by adequate and well-controlled studies. The failure of the Sponsor to offer legally and scientifically sufficient trial data should have been fatal to its NDA and now requires withdrawal of that approval.⁵⁸

approve an NDA at all, let alone to approve an NDA based on insufficient trial data. It is not uncommon at any stage of the NDA review process for FDA to require a drug sponsor to correct or amend an NDA by conducting properly designed and executed studies. Had the sponsor followed standard scientific norms and performed randomized, concurrently controlled trials comparing mifepristone-misoprostol abortion with surgical abortion it would have been able to supply comparative data.

⁵² See Opposition Comments at 8-9. Mifepristone-misoprostol abortions do not fall within either of these examples. Because surgical abortion, the standard of care, is the backup procedure if the Mifeprex Regimen fails, *ipso facto* the Regimen cannot be used to treat patients unresponsive to or intolerant of the standard of care.

⁵³ Furthermore, in this instance, the Sponsor did not attempt to test the drug in populations that it identified as intolerant or unresponsive and, indeed, the Mifeprex Regimen is not an option for patients unresponsive to or intolerant of surgical abortion because surgical abortion is the back-up procedure for Mifeprex patients.

⁵⁴ Opposition Comments at 9.

⁵⁵ NDA 20-785.

⁵⁶ The fact that leprosy is a rare disease in the U.S. makes it difficult to perform clinical trials. In addition, there are compassionate reasons for not awaiting the results of randomized, double-blinded comparator controlled clinical trials before treating patients suffering from leprosy. The fact that well-controlled trials were employed despite the existence of these mitigating factors is evidence of the value that the scientific community places on well-controlled trials.

⁵⁷ See Petition at 39 (discussing the thalidomide trials). In one study, all participants received either thalidomide or a placebo in addition to the standard dapsone treatment.

⁵⁸ See Petition at 30-35 (discussing statutory and regulatory requirements for clinical trials).

C. The Inclusion of Misoprostol in the Mifeprex Regimen Was Unlawful.

The Mifeprex Regimen combines the use of mifepristone and a second drug, misoprostol (Cytotec™). Although FDA never approved misoprostol as a stand-alone abortifacient, it approved misoprostol for use as an abortifacient in combination with mifepristone and mandated this use in the Mifeprex Package Insert. As explained in the Petition, FDA effectively sanctioned the use and promotion of misoprostol for an unapproved indication.⁵⁹ The promotion of an unapproved use contradicts the FD&C Act, which takes the position that “a drug manufacturer may not promote [its] product for any use other than the ones for which the company received FDA approval.”⁶⁰

In its Comment, the Sponsor defended the *de facto* approval of misoprostol for a new indication as an abortifacient and asserted that “FDA routinely approves drugs for use in combination with previously approved drugs without requiring any change in the labeling of the previously approved drug.”⁶¹ The Sponsor denied that this practice “puts either FDA or the sponsor of the later-approved drug in the position of ‘promoting’ off-label use of the previously approved drug.”⁶² The Sponsor offered four examples to support its position that this practice is not uncommon.⁶³

In fact, the Sponsor’s four examples support the position set forth in the Petition that subsequently approved drugs (Drug Bs – like Mifeprex) may reference previously approved drugs (Drug As – like misoprostol) on Drug B’s labeling only for *FDA-approved* indications.⁶⁴

⁵⁹ See Petition at 41-48. The drug’s manufacturer, G.D. Searle & Co. (“Searle”), did not file a supplemental NDA to obtain approval for misoprostol’s use as an abortifacient. Searle has subsequently been purchased, most recently, by Pfizer. See Petition at 42, n.188.

⁶⁰ 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, 645.

⁶¹ Opposition Comments at 9.

⁶² Opposition Comments at 10.

⁶³ Opposition Comments at 9-10.

⁶⁴ The first example offered by the Sponsor is the approval by FDA on September 10, 2001 of the combination of Xeloda (capecitabine) and Taxotere (docetaxel) for treating patients with metastatic breast cancer that has progressed after treatment with an anthracycline-containing cancer therapy. FDA initially approved Xeloda, an oral therapy, for the treatment of breast cancer on April 30, 1998, and FDA approved Taxotere, an intravenous product, for the treatment of advanced breast cancer on May 15, 1998. See FDA Press Release, “FDA Approves Xeloda in Combination with Taxotere for Advanced Breast Cancer” (Sept. 10, 2001) (available at: <<http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01101.html>>). Thus, when Xeloda and Taxotere are used together, each is being used for an FDA-approved use.

The Sponsor’s second example is FDA’s approval on July 15, 1999 of Actos to improve glycemic control in patients with Type 2 diabetes. Actos is indicated as a monotherapy and for use in combination with a sulfonylurea, metformin, or insulin “when diet and the single agent does not result in adequate glycemic control.” Letter, FDA/CDER to Mikihiro Obayashi, President, Takeda America Research & Development Center, Inc. (July 15, 1999). When used alone or together to treat Type-2 diabetes, each drug is being used for one of its FDA-approved indications.

Each example describes drug products that are being used in combination to treat indications approved for the single drugs at issue.

Upon close examination, the Sponsor's four examples underscore the fact that FDA's approval of mifepristone for use in combination with misoprostol, a drug never approved as an abortifacient, constitutes a significant departure from FDA precedents. As Professor Richard Merrill explained, "[i]n FDA's view, to promote any use of [its] new drug, the manufacturer must have agency approval – allowing that use to be included in the official labeling."⁶⁵ The approval in this instance struck at the heart of FDA's long-held policy that in order for a new drug use to be promoted, the drug's sponsor must submit an application seeking to demonstrate the safety and effectiveness of that new use.⁶⁶ It defies logic to imagine that Danco could be allowed to do with misoprostol what Searle could not do with its own drug – that is, promote an unapproved use of misoprostol. Yet, that activity is exactly what FDA permitted in Mifeprex's case. FDA's regulatory framework would be rendered toothless if third parties were permitted to behave in this manner.

In fact, Searle, which held the patent for misoprostol,⁶⁷ apparently *objected* to adding an indication for abortion to the Cytotec label. Searle's objections were overridden because only the combined regimen was effective. As the Sponsor explained, "[t]he fact is that mifepristone used as contemplated in 1983 was a failed drug – it was not sufficiently efficacious to have ever been approved."⁶⁸ Perhaps to avoid having to obtain Searle's cooperation, in an unprecedented

The Sponsor's third example is FDA's approval on October 26, 2001 of Viread (tenofovir disoproxil fumarate), a nucleotide reverse transcriptase inhibitor of HIV, for combined use with other antiretroviral agents for the treatment of HIV-1 infection in adults. The antiretroviral agents with which Viread is to be used have separately been approved for the treatment of HIV. Letter, FDA/CDER to Rebecca Coleman, Gilead Sciences, Inc. (Oct. 26, 2001) (NDA 21-356). The fact that Viread was not approved for use as a monotherapy in the treatment of HIV does not alter the analysis, but rather makes it a useful comparison for mifepristone, which has been approved as an abortifacient only in conjunction with misoprostol. Thus, when used together, each drug is being used for one of its FDA-approved indications.

The Sponsor offers as its fourth example FDA's approval of Nexium (esomeprazole magnesium) on February 20, 2001 for the treatment of erosive esophagitis and other symptoms associated with GERD (Gastroesophageal Reflux Disease). Letter, FDA/CDER to Kathryn D. Kross, AstraZeneca, LP (Feb. 20, 2001) (NDA 21-153; NDA 21-154). For one of its approved indications, *H. pylori* eradication, Nexium is used in combination with amoxicillin and clarithromycin, both of which have been approved for treating *H. pylori*. Thus, when they are used in combination with Nexium, each drug is simply being used for one of its approved indications.

⁶⁵ Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1766, n.40. As noted in the Petition, former FDA general counsel, Peter Barton Hutt, observed that FDA's actions with respect to misoprostol "set[] an extraordinary precedent" because FDA was "seemingly encouraging a drug's unapproved use." See Petition at 42-43 (Hutt's quotation was reported in Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1).

⁶⁶ 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).

⁶⁷ The patent for misoprostol has since expired, but at the time the Mifeprex Regimen was approved, Searle held exclusive rights to that patent.

⁶⁸ Population Council Response to the Request for Revision of the Regulatory Review Period Determination for MIFEPREX[®] Submitted by Concept Therapeutics Inc., Docket No. 01E-0363 (July 2, 2002): at 3 ("Sponsor's

“joint decision” in July 1994, FDA and the Sponsor “determined that the NDA need not cover misoprostol as well as mifepristone.”⁶⁹ The Sponsor subsequently explained, however, that “there can be no doubt that the approved human drug product contemplates both mifepristone and misoprostol, as shown in the approved labeling,”⁷⁰ which “specifically states that administration of mifepristone must be followed by administration of misoprostol.”⁷¹ The Sponsor added that “FDA has made clear on numerous occasions, FDA review of an NDA is ‘inextricably intertwined’ with the proposed labeling for the product.”⁷² In so stating, the Sponsor speaks out of both sides of its mouth – acknowledging that combined use with misoprostol is necessary for Mifeprex’s effectiveness and labeling, but “agreeing” with FDA that a corresponding misoprostol approval is not necessary.

Conclusion

In summary, the inclusion of misoprostol in the Mifeprex Regimen, outside of the NDA approval process for misoprostol, was unlawful. In order to reverse the extraregulatory approval of misoprostol as an abortifacient, FDA must withdraw its approval of the Mifeprex NDA.

D. Mifeprex-Misoprostol Abortions Are Not Safe.

The Sponsor continued in its Opposition Comments to defend the safety of Mifeprex, but has not allayed the concerns set forth in the Petition.⁷³ Rather than address the scientific and medical issues raised in the Petition, the Sponsor has mischaracterized them. As discussed above, the trials submitted by the Sponsor to support its NDA did not establish the safety of mifepristone-misoprostol abortions, and post-approval data on the Regimen have done no better - serving only to raise the Petitioners’ concerns about the safety of the Mifeprex Regimen.

1. FDA Determined that Mifeprex Would Be Unsafe without Restrictions.

FDA approved mifepristone under the restricted distribution prong of Subpart H, which FDA reserves for drugs that “can be used safely only if distribution or use is modified or restricted.”⁷⁴ Accordingly, the Mifeprex Regimen includes a number of restrictions.⁷⁵ As the

Response to Corcept”). In this document, the Sponsor responded to Corcept’s June 10, 2002 request that FDA consider 1983 rather than August, 4, 1994 as the starting date for the regulatory review of the Mifeprex investigational new drug application (“IND”). The Sponsor sought to convince FDA that the appropriate period for determining patent length began on August 4, 1994, the date of the IND that allowed for the investigation of mifepristone plus misoprostol to induce abortions. The Sponsor did not obtain the patent extension that it sought. The initial ruling in the Population Council’s favor was reversed by FDA. *See Note, Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex; Amendment*, 67 Fed. Reg. 65358 (Oct. 24, 2002).

⁶⁹ Sponsor’s Response to Corcept at 2.

⁷⁰ Sponsor’s Response to Corcept at 3.

⁷¹ Sponsor’s Response to Corcept at 2.

⁷² Sponsor’s Response to Corcept at 2-3 (citation omitted).

⁷³ *See* Opposition Comments at 10-14.

⁷⁴ *Subpart H Final Rule*, 57 Fed. Reg. at 58942 (“Summary”).

Petition explained, however, these restrictions were inadequate to make the drug safe.⁷⁶ Moreover, the Sponsor never acknowledged the inherent dangers posed by the approved Mifeprex Regimen, balked at implementing distribution restrictions, and dismissed out of hand the challenges about the adequacy of the restrictions to reduce the dangers of the Mifeprex Regimen.⁷⁷ Now that it has FDA's imprimatur to market the drug, the Sponsor takes minimal, if any, actions to carry out the required restrictions.⁷⁸

Additionally, FDA's final decision to omit key restrictions from the approved Regimen has subjected patients who use the Mifeprex Regimen to unnecessary risks. A pre-procedure ultrasound, for example, is necessary to evaluate the gestational age because the Mifeprex Regimen has been shown to be less effective and riskier to the patient as gestational age increases.⁷⁹ Ultrasound is also necessary to identify women whose pregnancies are ectopic and who should not undergo the Mifeprex Regimen.⁸⁰ Further, because complications and failures are common and predictable and can seriously endanger the health of the patient, FDA should

⁷⁵ For a list of the restrictions, *see* Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 2 ("Mifeprex Approval Letter"). The Sponsor contends in its Opposition Comments that it cooperated with FDA by proposing restrictions. *See* Opposition Comments at 10-11. This contention reflects the Sponsor's failure to distinguish between restrictions on the distribution of a drug to prescribing physicians and restrictions designed to ensure patient safety. Furthermore, contrary to the Sponsor's suggestion that decisions about the restrictions in the Mifeprex Regimen were the product of "discussion, negotiation, give and take, debate, even on occasion disputes, between FDA and the Sponsors [that] is characteristic of the review process for many drugs" (Opposition Comments at 11), the Sponsor went to great lengths to avoid including safety restrictions in the Mifeprex Regimen. In fact, after the Sponsor failed to suggest appropriate restrictions to protect Mifeprex patients, FDA proposed its own set of restrictions. Then, the Sponsor complained publicly about the allegedly onerous restrictions. FDA relented and inappropriately eliminated a number of key restrictions. *See* Petition at 49-57 for a discussion of the development of and the Sponsor's opposition to safety restrictions.

⁷⁶ *See* Petition at 57-65.

⁷⁷ *See* Opposition Comments at 10. The Petition did not assert that the approved regimen must exactly follow the regimen employed during the trials. Nevertheless, if trials include important safeguards that are omitted from the approved regimen, then the relevance of the data generated by those trials is undermined. For this reason, a trial should be designed to reflect the anticipated conditions under which a drug will be used. *See* Petition at 75-76. For example, had the Sponsor designed the trial to reflect anticipated conditions of use, misoprostol probably would have been administered vaginally during the trials, which appears to be the standard method of administration now that the Mifeprex Regimen is approved. Had the trial protocol called for vaginal administration, it would have drawn attention to the unlawful inclusion of misoprostol in the Regimen because misoprostol is approved only for *oral* use. As FDA has explained, "[i]n order to change or add a new dosing regimen to the labeling, the sponsor must submit data to FDA from clinical trials that show the new regimen is safe and effective." *See* FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol virginally at different doses?") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm>).

⁷⁸ *See* Section I.D.3, herein.

⁷⁹ *See* Spitz Article at 1241 ("Results").

⁸⁰ The Sponsor's Opposition Comments addressed the use of ultrasound only for the purpose of dating pregnancies. As explained in the Petition, ectopic pregnancies cannot be treated by the Mifeprex Regimen and the symptoms of ectopic pregnancy are likely to be mistaken as the normal effects of undergoing a Mifeprex abortion. For a more complete discussion of the necessity of using ultrasound to identify ectopic pregnancies, *see* Petition at 60-61.

have required prescribing physicians to be trained in mifepristone-misoprostol administration and surgical abortions and to have *admitting* privileges at a nearby emergency facility.⁸¹

FDA determined that Subpart H restrictions were necessary because, without them, mifepristone-misoprostol abortions were not safe. Thus, the Petitioners' concerns with the Regimen's safety rest on the belief that the weakness of the Regimen's restrictions is inconsistent with FDA's decision to approve the drug under Subpart H.

2. Post-approval Evidence Confirms that the Approved Distribution Restrictions Were Insufficient to Adequately Protect Patients.

The Sponsor's analysis inaccurately characterized the post-approval experience with the Mifeprex Regimen.⁸² A number of life-threatening adverse events experienced by Mifeprex patients caused FDA to work with the Sponsor to issue a letter to health care providers.⁸³ The

⁸¹ In fact, FDA proposed to include such restrictions in the Mifeprex Regimen. The set of restrictions proposed by FDA on June 1, 2000, would have required physicians prescribing Mifeprex to be "trained and authorized by law" to perform surgical abortions, to be trained in administering the Mifeprex Regimen and handling resulting adverse events, and to 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." 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].

⁸² Opposition Comments at 10, 13-14. The Sponsor pointed to a recent article authored by the medical director of Danco, Dr. Richard Hausknecht, as evidence that Mifeprex is safe. See Opposition Comments at 10 (citing Hausknecht Article); regarding Dr. Hausknecht, see also Petition at 71, n.309. Unfortunately, the article, which reports on the drug's use in the United States since approval, relies on data that are incomplete and of questionable quality. First, reliable data as to the number of patients who have undergone the Mifeprex Regimen is not available. Dr. Hausknecht used a figure of 80,000, which was derived from "sales figures [for Mifeprex] and known patterns of mifepristone utilization." Hausknecht Article at 464. This number may be too high as it may not take into account drugs that were ordered but not used. Second, the number of adverse events reported is likely to be significantly underestimated. Abortion clinics, which (according to Dr. Hausknecht's estimates) carried out approximately 90% of Mifeprex abortions, may have a disincentive to report adverse events from a procedure that they promote and may be less likely than physicians in private practice to report adverse events. In addition, it is likely that many patients were lost to follow up. In the U.S. Clinical Trial, 106 of the 2,121 patients (or nearly 5%) did not return for their third required visit. A higher "lost to follow up" number is to be expected outside of the clinical setting. Finally, the article's descriptions of the adverse events that were reported generally appear to be incomplete and tend to downplay any possible connection with the Mifeprex Regimen. For example, the article explained that a twenty-one year old woman had suffered a coronary artery occlusion five days after she received misoprostol. See Hausknecht Article at 464, col. 2. The article provided few details about her Mifeprex abortion and pointed to her "strong family history of heart disease" without also mentioning that there are no data on the safety of the Mifeprex Regimen in women with cardiac problems and these women were excluded from the Clinical Trials. In sum, an objective assessment of the safety and efficacy of mifepristone-misoprostol abortions would require a concurrently-controlled, randomized comparison of a mifepristone-misoprostol regimen reflecting actual conditions of use with surgical abortion. The Sponsor did not conduct or provide data from such trials in support of its application and Dr. Hausknecht's article – a very general overview without the first-hand, patient-level detail necessary to scientifically assess the safety of the Mifeprex Regimen – does not fill this void.

⁸³ 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>).

Petition discussed these life-threatening adverse events which included ruptured ectopic pregnancies, serious systemic bacterial infections, and a coronary event.⁸⁴ The Sponsor, in its Opposition Comments, insisted that “FDA has not found any causal connection” between the Mifeprex Regimen and these adverse events.⁸⁵ However, the clear implication of the issuance of the Dear Doctor Letter and FDA’s accompanying “Questions and Answers” is that such a causal link does exist.

The serious adverse events reported to date are consistent with concerns about the drug regimen that were expressed prior to the approval.⁸⁶ The recent death of Holly Patterson, an eighteen year old from Livermore, California, unfortunately epitomizes the concerns of the Petitioners.⁸⁷ According to Ms. Patterson’s father, at the time of his daughter’s death, she was terminating her pregnancy with a Mifeprex Regimen prescribed by the Planned Parenthood in Hayward, California. Apparently, Ms. Patterson started the abortion procedure on Wednesday, September 10, 2003, by taking mifepristone tablets. On Saturday, September 13, 2003, she apparently took the misoprostol that the clinic had given her. By Sunday she was having such severe cramping and bleeding that her boyfriend took her to the emergency room. Ms. Patterson received pain killers and was sent home, but she continued to bleed severely and experienced acute pain that prevented her from walking. Early Wednesday, September 17, 2003, Ms. Patterson’s boyfriend took her back to the emergency room, where she died that afternoon.

According to Mr. Patterson, the doctor told him that his daughter “hadn’t aborted all the fetus, and she had fragments left in her, and she had a massive systemic infection and went into septic shock.”⁸⁸ The results of the coroner’s investigation are not expected to be released for several months, but Ms. Patterson’s apparent death of a serious systemic bacterial infection is not the first such death since FDA approved Mifeprex. As noted above, the Dear Doctor Letter

⁸⁴ See Petition at 65-71. As the number of mifepristone-misoprostol abortions rises, the number of serious adverse events associated with these abortions is likely to increase as well. Because the normal progression of the Mifeprex Regimen is characterized by prolonged bleeding, the patient bears the responsibility for determining how much bleeding is excessive and whether she needs to seek medical assistance. Health care providers who are not experienced providers of abortion, generally, or mifepristone-misoprostol abortions, specifically, may be poorly equipped to assist the patient in determining whether medical intervention is necessary, let alone to provide the needed medical intervention.

⁸⁵ See Opposition Comments at 13.

⁸⁶ See *Americans United for Life et al.*, Citizen Petition (Feb. 28 1995) (requesting FDA’s consideration of a number of potential hazards of mifepristone-misoprostol abortions) [FDA FOIA Release: MIF 006144-6248].

⁸⁷ Julian Guthrie, “Pregnant Teen’s Death Under Investigation; East Bay Woman Had Taken RU-486, According to Father,” *San Francisco Chronicle* (Sept. 19, 2003): at A21 (available at: <http://www.sfgate.com>). See also Gina Kolata, “Death at 18 Spurs Debate Over a Pill for Abortion,” *New York Times* (Sept. 24, 2003): at A24 (“There were 264 adverse reactions, including infections, bleeding, allergic reactions and tubal pregnancies.”).

⁸⁸ *Id.* See also Julian Guthrie, Sabin Russell, and Katherine Seligman, “After Daughter’s Death, Father Wants Close Look at RU-486; Abortion Pill’s Safety Defended by Doctors as Better than Surgery,” *San Francisco Chronicle* (Sept. 20, 2003): at A17 (available at: <http://www.sfgate.com/cgi-bin/article.cgi?file=/chronicle/archive/2003/09/20/BA310011.DTL>) (“Patterson said the attending physician at Pleasanton’s Valley Care Medical Center told him his daughter had died of septic shock – a severe bacterial infection. ‘The doctor told me she had fragments of the fetus still left in her uterus and that caused the infection.’”).

reported “[t]wo cases of serious systemic bacterial infection (one fatal).”⁸⁹ The presence of retained products of conception can lead to the development of intrauterine or systemic infection, and it is possible that mifepristone could potentiate this possibility via negative effects on immune system function or normal protective mechanisms.⁹⁰

In addition to questions about Mifeprex causation in this case, questions also have been raised about the role that Ms. Patterson or her local hospital emergency room may have played in contributing to her death.⁹¹ These questions cannot be answered without recognizing that patients and emergency room physicians may be unable to distinguish the normal progress of the Regimen from a life-threatening situation. Consequently, it is not at all clear that emergency rooms will be able to rescue dangerously ill Mifeprex patients from the peril in which they have been placed by the Regimen. Consider the plausible scenario described in the footnote below.⁹² The severity of the reported adverse events requires FDA action to remove Mifeprex from the market.

⁸⁹ Dear Doctor Letter at 1. The fatality apparently precipitated a halt in the Population Council’s clinical trials of mifepristone in Canada.

⁹⁰ Given the nature of the Mifeprex Regimen, the embryo or other products of conception will not be expelled from the uterus in a number of cases. It is well known that the presence of retained necrotic products of conception can lead to intrauterine and systemic infection. Furthermore, it is possible that mifepristone itself may alter the local immune response at the level of the endometrium or the cervix. There are numerous alterations of the immune system during pregnancy, and progesterone can affect immune system function. Therefore, it is plausible that a progesterone receptor antagonist like mifepristone could negatively affect the normal immune system within the uterus, or compromise antibacterial mechanisms of the cervix, making a woman more susceptible to infection. *See, e.g.*, World Health Organization (WHO), “Pregnancy Termination with Mifepristone and Gemeprost: A Multicenter Comparison between Repeated Doses and a Single Dose of Mifepristone,” 56 *Fertility & Sterility* 32-40 (1991) (29.4% of patients with incomplete abortion compared with 2.6% of those with complete abortion received antibiotics during a six week follow-up period for suspected genitourinary infection; both groups combined accounted for 3.9% of the total study population).

⁹¹ *See, e.g.*, Gina Kolata, “Death at 18 Spurs Debate Over a Pill for Abortion,” *New York Times* (Sept. 24, 2003): at A24 (“But it is unclear what happened to Holly Patterson. Did she have enough medical supervision while taking the pills? When did she seek medical attention? Did she wait until it was too late? Did she tell the doctors in the emergency room that she had taken mifepristone? Why, in fact, did she die?”).

⁹² A patient comes to the emergency room complaining of significant pelvic pain and cramps. She reports that she has taken Mifeprex and misoprostol for a medical abortion. At this time, she has no significant change in vital signs (*i.e.*, no fever or very low grade fever – which can be related to misoprostol – and no significant tachycardia, etc.). The emergency room physician, knowing that this drug combination normally causes cramping at this stage in the process, assumes she has a personal low pain tolerance threshold, and, therefore, gives her pain medications to try to alleviate her discomfort until the abortion completes. However, the patient may be in the early stage of an intrauterine infection even though she is not yet manifesting other signs of that condition aside from pain and bleeding which are both part of the Mifeprex abortion process. At this stage, the emergency room physician has no good way to detect that an infection has begun. Furthermore, even if the emergency room physician found evidence of retained tissue in the uterus, the physician would not be surprised or alarmed by that discovery given the nature of mifepristone-misoprostol abortions. Unless the patient had significant hemorrhaging or evidence of infection, no intervention would be necessary or even warranted since one would presume that the abortion was going according to plan at that juncture (recall that bleeding can last up to several weeks duration). So to continue this hypothetical scenario, the patient goes home, and the infection subsequently becomes systemic. The patient goes into septic shock and is not able to be saved by the time she re-presents to the emergency room. It would not be surprising if Ms. Patterson’s death followed such a course given statements made to the press by her father. In this credible scenario the Mifeprex Regimen, after having placed her in great danger, effectively camouflaged the seriousness of her condition from the emergency room physician.

Furthermore, FDA cannot rely on the “spotty” reporting of adverse events for the Mifeprex Regimen. The usual flow of post-approval adverse event information will not be forthcoming for this drug. It is questionable whether individual lawful distributors of Mifeprex, who tend to be outside the mainstream pharmaceutical wholesale distribution industry, will routinely report adverse events to FDA.⁹³ Also, because the drug is intended to be administered in physicians’ offices, a pharmacist is unlikely to dispense the product or hear of drug-drug and drug-food interactions, or other adverse events. Moreover, the types of facilities that provide medical and surgical abortions are often staffed with social-work counselors and health care workers who are not medical doctors and have limited medical training. As such, they may be unfamiliar with the adverse event reporting procedure for medical professionals (*i.e.*, MedWatch).

Even for properly-licensed physicians, FDA’s MedWatch reporting is voluntary.⁹⁴ Since privacy issues are often the primary concern of women who seek abortions, a physician may not file a MedWatch report in order to protect patient confidentiality. Accordingly, the Petitioners are concerned about the possibility that medical complications are not being reported. Finally, it is possible that other women who have suffered adverse events during a mifepristone-misoprostol abortion have sought assistance from crisis pregnancy centers, counselors, and charitable organizations,⁹⁵ which may not be familiar with the MedWatch reporting system. Given the foregoing, the Petitioners believe that FDA’s continuing review of the safety profile of Mifeprex relies improperly on an incomplete database of post-approval adverse events.

3. The Sponsor Has Failed to Require Adherence to the Restrictions.

The Sponsor insisted that it “will continue, as [it] always intended, to honor [its] commitments to carry out the program of restrictions imposed in the approval letter.”⁹⁶ Yet, the Sponsor has broken its promise. The Sponsor apparently has not taken steps to ensure that Mifeprex is used in accordance with the approved Regimen and has continued to distribute the drug to providers that depart from the Mifeprex Regimen. For instance, the Sponsor has asserted, in its Opposition Comments, the erroneous position that the guidelines in the Prescriber’s Agreement “do not state any specific dose or regimen for prescribing Mifeprex”⁹⁷ The Sponsor’s statement reflects only one example of its continuing refusal to accept even FDA’s minimal restrictions issued pursuant to Subpart H.

⁹³ Obviously, distributors of mifepristone who are outside the lawful channels of distribution are even less likely to report adverse events.

⁹⁴ See <<http://www.fda.gov/medwatch/report/hcp.htm>>.

⁹⁵ *Consider Estate of Brenda Vise vs. Volunteer Women's Medical Clinic, L.L.C., et al.* (Circuit Court of Hamilton County, Tennessee, filed August 14, 2002); *Danlin Tang, Albert Ng vs. Dr. Soon Chon Sohn, Family Planning Associates Medical Group, and Does 1 – 50* (Superior Court of the State of California for the County of Los Angeles, Central District, notice to file dated December 13, 2002).

⁹⁶ Opposition Comments at 6.

⁹⁷ Opposition Comments at 14.

In the face of this recalcitrance, FDA should exercise its enforcement authority, investigate the Sponsor's failed commitments under its NDA approval, and take appropriate action, as it has in other cases where risk management programs were deemed insufficient to protect patients.⁹⁸ We note that, contemporaneous with the issuance of the Sponsor's Dear Doctor Letter, FDA underscored the possibility that if providers "do not follow the agreement, the distributor may discontinue distribution of the drug to them."⁹⁹ Shortly after approving Mifeprex, the Agency wrote to a member of Congress and stated, "If restrictions are not adhered to, FDA may withdraw approval."¹⁰⁰

Even assuming that the Sponsor's responsibilities extend only as far as ensuring that the prescriber is adhering to the Prescriber's Agreement, the Sponsor is failing to meet its due diligence obligation.¹⁰¹ The Prescriber's Agreement requires, *inter alia*, that the prescriber "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 them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself."¹⁰² The Patient Agreement, which both the patient and the prescriber sign, states that the patient "believe[s] I am no more than 49 days (7 weeks) pregnant."¹⁰³ Yet numerous prescriber websites advertise the Mifeprex Regimen as being available for patients whose pregnancies have progressed beyond 49 days.¹⁰⁴ The Patient

⁹⁸ For example, GlaxoSmithKline voluntarily withdrew its NDA for Lotronex (alosetron hydrochloride) rather than accept restrictive risk management guidelines involving informing patients of risks, limiting access to closely monitored patients, and continued clinical research. See "FDA and Glaxo Still Working on Lotronex's Return," *Dickinson's FDA Webview* (Jan. 24, 2002). Bayer voluntarily withdrew Baycol (cerivastatin) after reports of deaths due to severe rhabdomyolysis, when risk management efforts of labeling changes and "Dear Healthcare Provider" letters had little impact on physicians who continued to prescribe the drug at unrecommended higher doses. See "31 Baycol-related Deaths Cause the Drug's Withdrawal," *Dickinson's FDA Webview* (Aug. 8, 2001). Warner Lambert withdrew Rezulin (troglitzone) at FDA's urging after label restrictions and recommended monitoring of liver function failed to control inappropriate prescribing. See "Rezulin Withdrawal a Defeat for FDA 'Labeling Can Do It' Theory," *Dickinson's FDA Webview* (Mar. 21, 2000).

⁹⁹ See FDA Q & As at Question 12.

¹⁰⁰ 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].

¹⁰¹ See Opposition Comments at 14-15.

¹⁰² Mifeprex™ (Mifepristone) Tablets, 200 mg Prescriber's Agreement ("Prescriber's Agreement").

¹⁰³ See Item 4 of the Patient Agreement Mifeprex (mifepristone) Tablets ("Patient Agreement"). In addition, the Mifepristone Medication Guide ("Medication Guide") states that you should not take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began."

¹⁰⁴ See, e.g., All Women's Health Centers website (available at: <http://www.floridaabortion.com/services_abortion/nonsurgical.shtml>) (visited Sept. 5, 2003) ("Non-surgical abortions, sometimes called 'medical abortions,' are performed in the first 9 weeks of pregnancy. Non-surgical abortion can be administered in pill form (otherwise known as Mifeprex or RU-486)."); Family Planning Associates Medical Group, Phoenix and Tempe Arizona, (available at: <<http://www.fpamg.com/medical.html>>) (visited Sept. 5, 2003) (noting that Mifeprex Regimens are "done until the 56th day of pregnancy"); Planned Parenthood Golden Gate (available at: http://www.ppgg.org/medical/abortion_medical.asp) (visited Oct. 1, 2003) ("Medical abortion is a way to end pregnancy without surgery. It is done with medications up to 63 days after the last period begins."); Seattle Medical and Wellness Clinic (available at: <<http://www.smawc.com/html/services.html>>) (visited Sept. 5, 2003) (including following description: "**Medical Abortion (9 weeks LMP or less):** We offer non-surgical abortion with Mifeprex (a.k.a. the Abortion Pill, RU486) and Cytotec (misoprostol).").

Agreement also states that the patient “will take misoprostol in [her] provider’s office two days after [she] take[s] Mifeprex (Day 3).”¹⁰⁵ Yet many prescribers’ websites indicate that patients take misoprostol at home rather than at the provider’s office.¹⁰⁶ The discrepancies between the marketplace regimen being prescribed and the approved Regimen that the patient agrees to follow indicate that many prescribers are allowing patients to make false statements. Under its NDA duties, the Sponsor has an obligation to conduct due diligence about the prescribers to whom it sells Mifeprex, and it must stop those sales if the approved Regimen is breached. Furthermore, the Sponsor has a duty to keep records of these stopped distributions.¹⁰⁷

Given that these discrepancies are freely published on prescriber websites, the Sponsor should be aware of them.¹⁰⁸ Therefore, the Sponsor knowingly continues to supply prescribers who are not following the guidelines in the Prescriber’s Agreement. These prescribers are knowingly eviscerating the requirements to provide patients with the Medication Guide, to

¹⁰⁵ See Patient Agreement, Item 6. In addition, the Medication Guide states that the patient “**must return** to [her] provider on Day 3 and about Day 14” (emphasis in original).

¹⁰⁶ See, e.g., Family Planning Associates Medical Group, Phoenix and Tempe Arizona, (available at: <<http://www.fpamg.com/medical.html>>) (visited Sept. 5, 2003) (explaining that “[t]he patient inserts 4 tablets of Misoprostol into the vagina at home 2-3 days” after ingestion of Mifeprex); Little Rock Family Planning website <<http://www.lrfps.com/RU486.html>> (visited Sept. 5, 2003) (describing the regimen employed by the clinic, which is “one of these regimens [sic] which has been shown to be safe and is more convenient for women using the method”: “**Step Two, at home (or motel)** ... Six to 8 hours after the mifepristone pills have been swallowed 8 Cytotec tablets are placed in the vagina. **Step Three, this will depend on how far you live from our clinic:** A) *If you live within one hour of Little Rock* ... If you have not passed the pregnancy by 24 hours after you put the Cytotec tablets in your vagina, you will put a [sic] 4 tablets in your vagina and still plan to keep your appointment for the following week. B) *If you live outside the Little Rock Area* ... You will return at 9AM the following morning to have an ultrasound to see if the abortion is complete. If the abortion is complete you will be discharged home and asked to take a urine pregnancy test in 3 weeks. ... If you have not had a complete abortion you will be given 4 Cytotec [sic] to place in your vagina ... ”); Planned Parenthood Golden Gate (available at: <http://www.ppgg.org/medical/abortion_medical.asp>) (visited Oct. 1, 2003) (“Medical abortion using Mifepristone involves three steps. First, the doctor will give you mifepristone pills, which block progesterone, a hormone needed to maintain pregnancy. Two days later, as directed by your clinician, you will insert another medication called misoprostol as a vaginal suppository. Misoprostol causes the uterus to contract and empty which completes the abortion. Finally, women must return to the clinic a few days after taking the misoprostol for a follow-up.”); Women’s Health Practice website (available at: <<http://www.womenshealthpractice.com/abortion.htm>>) (visited Sept. 5, 2003) (explaining, as part of the medical abortion regimen that the clinic describes as “most similar to the FDA-approved regimen,” that “[t]he misoprostol will be provided to you with medication instructions that carefully explain the timing and route of administration.”).

¹⁰⁷ 21 C.F.R. § 314.81(b)(2) (requiring NDA sponsors to submit an annual report describing distribution data). State or federal agencies may need these data if patient deaths continue and the public outcry (and/or the plaintiffs’ lawyers bar) demand investigations.

¹⁰⁸ The Petition set forth a number of examples of Mifeprex provider websites that advertised noncompliance with the approved Mifeprex Regimen. See Petition at nn. 309, 313, 315, 317. Since the submission of the Petition, these websites have not been altered. (These websites were visited most recently on September 5-7, 2003. One of the website addresses changed and its content was updated, but it still states that “at home, the patient will insert four tablets [of misoprostol] into her vagina.” See <http://www.presidentialcenter.com/services_nonsurgical.html> (visited Sept. 7, 2003)). It appears, therefore, that the Sponsor, alerted by the Petition to these instances of noncompliance, has not taken any steps to require compliance with the approved regimen. Dr. Hausknecht, the medical director of Danco, operates one of the websites that continues to advertise a regimen that differs from the approved regimen. See <<http://www.safeabortion.com/procedure.htm>> (visited Sept. 7, 2003).

obtain their signatures on the Patient Agreement, and to give them the opportunity to read and discuss these documents. The Patient Agreement is intended by FDA to describe the Mifeprex Regimen as approved and to obtain the patient's informed consent to adhere to the approved Regimen, all for the protection of the patient. Instead, some prescribers, with the Sponsor's tacit approval, are permitting patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements. In the face of such evidence, the Sponsor cannot be described as meeting its obligations with respect to the restrictions on Mifeprex.

Conclusion

Women are being told that Mifeprex is safe even if it is used in a manner different from the Regimen approved by FDA. This is a cavalier approach to distributing a drug that was deemed by FDA to be too dangerous to approve without restrictions. The Sponsor's refusal to restrict distribution to physicians who adhere to the approved Regimen represents the continuation of a pattern of overlooking the risks to women's health posed by Mifeprex. FDA should halt the marketing of this unsafe drug.

E. The Sponsor's Revised Phase IV Commitments Are Inadequate.¹⁰⁹

The Sponsor's Opposition Comments downplayed the significance of the changes prior to approval in the Sponsor's Phase IV commitments.¹¹⁰ As noted in the Petition, those changes by the Sponsor relegated certain study objectives to secondary status, eliminated the commitment to study the long-term effects of multiple uses of the Regimen, and weakened the commitment to monitor the adequacy of the distribution and credentialing system.¹¹¹

The Sponsor's insistence that the range of topics to be studied was not narrowed contradicts statements made by the Sponsor when it proposed modifications of its Phase IV commitments in September 2000.¹¹² The Sponsor, citing feasibility concerns, decided not to study the long-term effects of multiple uses of the Mifeprex Regimen.¹¹³ Moreover, combining multiple study objectives into one study reduced the value of the data that would be generated

¹⁰⁹ The Petitioners requested, pursuant to FOIA, information about the Phase IV Mifeprex study protocols and any data arising from the Phase IV studies submitted by the Sponsor. *See* FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001). To date, the Petitioners have not received any responsive information.

¹¹⁰ *See* Opposition Comments at 15-16. *See also* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 15, 2000): at 1 [FDA FOIA Release: MIF 001326] (committing to conducting two Phase IV studies).

¹¹¹ *See* Petition at 84-88.

¹¹² *See* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 5 [FDA FOIA Release: MIF 001333-49] ("As new data have become available, some of the studies originally proposed have become unnecessary. Other studies, on reflection, seem unlikely to gather useful data at any reasonable cost or, in some cases, at any cost.").

¹¹³ *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 7 ("Mifeprex Approval Memo"). As discussed in the Petition, the Sponsor, in asking for the elimination of this commitment, was motivated in part by concerns that conducting such a study would be burdensome for the Sponsor – a reason that is not generally persuasive with FDA. *See* Petition at 87.

with respect to the secondary study objectives.¹¹⁴ Given the importance of understanding the effect of a patient's age, the effect of a patient's smoking status, the rate of patient follow-up on Day 14, and the adequacy of the distribution and credentialing system, the Sponsor should not have been permitted to accord these study objectives secondary status.

The Sponsor defended the changes in the study requirements by citing FDA's approval memorandum for the proposition that the changes in the Phase IV Study commitments reflected changes to the distribution system and labeling.¹¹⁵ The Sponsor's argument is misleading. By allowing the distribution of mifepristone to physicians who could not provide surgical intervention, an immediate need arose to study the effect of that major change;¹¹⁶ accordingly, FDA added a primary study requirement.¹¹⁷ However, the September 2000 changes in distribution and labeling should have not have reduced or eliminated other primary Phase IV study commitments that were not related to the distribution or labeling changes.

Conclusion

FDA inappropriately granted the Sponsor's request to reduce its original Phase IV commitments. As a consequence, key questions about the safety of the Mifeprex Regimen will remain unanswered.

F. The Approval of Mifeprex Without Supporting Pediatric Data Was Both Unlawful And Imprudent.

In its Opposition Comments, the Sponsor admitted that it did not conduct clinical studies in the pediatric population, but relied instead on an FDA "waiver" of pediatric testing. Yet, the FD&C Act and FDA's approval regulations for NDAs require safety and effectiveness testing to support a new drug's indications for use. In a case where the Sponsor does not intend to restrict the drug's use in the pediatric population, FDA has only limited authority to cede the requirement for pediatric testing. In the case of Mifeprex, FDA's decision to approve the NDA without pediatric data was arbitrary, capricious and unlawful agency action.

¹¹⁴ Specifically, the effects of age and smoking status and the frequency with which patients return for follow-up on Day 14 were to be studied as part of "[a] cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compare to physicians who refer their patients for surgical intervention." See Petition at 86 (citing Mifeprex Approval Letter at 3). Furthermore, this study would be the only Phase IV study of another objective originally slated to be the focus of a separate Phase IV study, namely the adequacy of the distribution and credentialing system. See *generally* Mifeprex Approval Memo at 7.

¹¹⁵ See Opposition Comments at 15-16 (citing Mifeprex Approval Memo at 7).

¹¹⁶ This change was deemed significant enough to require the addition of a "black box" warning to physicians who could not perform surgical abortions. The black box warning directed them to make arrangements for the provision of emergency surgical intervention.

¹¹⁷ FDA correctly noted the need for a new study objective when it approved this change: "To ensure that the quality of care is not different for patients who are treated by 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, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study." Mifeprex Approval Memo at 5.

1. FDA's NDA Approval Regulations Required Pediatric Data.

The law is clear that the clinical studies used to support an NDA must establish the drug's safety and efficacy for the proposed conditions of use. Under the FD&C Act, a person may file an NDA requesting FDA approval of a new drug provided that the NDA contains, in relevant part, "full reports of investigations which have been made to show whether or not such drug is safe *for use* and such drug is effective *in use*" ¹¹⁸ Likewise, FDA's NDA approval regulations require "a description and analysis of each controlled clinical study *pertinent to a proposed use* of the drug." ¹¹⁹ This testing requirement exists separately from the so-called "Pediatric Rule," ¹²⁰ which also delineates pediatric testing requirements.

The Petitioners acknowledge that, as of October 17, 2002 and for the time being, FDA is enjoined from enforcing the Pediatric Rule. ¹²¹ However, the Petitioners challenge the Sponsor's contention that the issue of FDA's proper administration of the Rule is moot, in light of the *AAPS* court's decision to grant an appeal of the case, which is now pending. ¹²² Rather, the Mifeprex NDA was subject to the Pediatric Rule, which was finalized and became effective while FDA was reviewing the NDA, ¹²³ and FDA should have administered it properly ¹²⁴ or waived it properly. ¹²⁵

¹¹⁸ 21 USC § 355(b)(1)(A) (emphasis added).

¹¹⁹ 21 C.F.R. § 314.50(d)(5)(ii) (emphasis added).

¹²⁰ 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) (testing requirements set forth in 21 C.F.R. § 314.55). See also Petition at 76-83 (discussing Pediatric Rule).

¹²¹ *Association of American Physicians and Surgeons v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002) ("*AAPS*").

¹²² The Elizabeth Glaser Pediatric AIDS Foundation and the American Academy of Pediatrics filed a motion to appeal on December 16, 2002. See Docket for Case No. 00-CV-2898 (entry no. 73).

¹²³ The Pediatric Rule was promulgated on December 2, 1998 and became effective on April 1, 1999. FDA reviewed the Mifeprex NDA from March 18, 1996 until September 28, 2000, when it was approved.

¹²⁴ Under the Pediatric Rule, FDA's treatment of the Mifeprex NDA was improper, in part, because the agency did not require the Sponsor to submit supporting pediatric data. The regulation stated that, "where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults *usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.*" 21 C.F.R. § 314.55(a) (emphasis added). This requirement also was articulated earlier by FDA in the Prescription Labeling regulation. See 59 Fed. Reg. 64240 (Dec. 13, 1994); 21 C.F.R. § 201.57(f)(9)(iv). As noted elsewhere in this Response, the Petitioners also question whether the Sponsor's adult data were derived "from adequate and well-controlled studies."

¹²⁵ It should be noted that even if FDA concluded that pediatric effectiveness of the Mifeprex Regimen could be extrapolated from adult studies, this would not be an appropriate ground for an actual *waiver* of the Pediatric Rule. The Pediatric Rule provides three grounds for waiver from the obligation imposed by the rule on drug sponsors to demonstrate that their drug is safe and effective for pediatric patients. 21 C.F.R. § 314.55(c). In some instances, drug sponsors are able to provide sufficient adult data, usually supplemented by pediatric-specific data, from which pediatric safety and efficacy can be extrapolated. 21 C.F.R. § 314.55(a). FDA stated that it was waiving the pediatric rule with respect to Mifeprex, yet did not cite to any of the bases for waiver provided in paragraph (c) of the Pediatric Rule. Mifeprex Approval Letter at 3. For a comprehensive discussion on the ineligibility of Mifeprex for a waiver from the Pediatric Rule, see the Petition at 78-82.

Irrespective of the current status of the *AAPS* case, at the time of the approval of the Mifeprex NDA the Agency was obligated to meet the requirements of its NDA approval regulations. FDA erred in its failure to require the Sponsor to submit pertinent pediatric data and to assess those data in its review of the NDA for Mifeprex. In so doing, the Agency abrogated its role of protecting and promoting the public health and safety. This constitutes the type of “arbitrary and capricious” action that is generally prohibited under the Administrative Procedures Act (“APA”).¹²⁶

2. The Drug’s Expected Conditions of Use Included the Pediatric Population.

Mifeprex is intended for use by menstruating females. The drug’s labeling states “Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days’ pregnancy.” Nothing in the “Indication and Usage” section of the labeling limits the drug’s use to adults.¹²⁷ Likewise, Danco’s marketing claims are not targeted to a particular age group, such as women “over age 18.” The patient population therefore logically includes all females who can become pregnant – that is, as of the age their first menstrual period begins (*i.e.*, “menarche”) until they no longer have a menstrual period (*i.e.*, “menopause”). According to FDA, the average age of menarche in the United States is 12 years, although menstruation may commence in healthy females as early as age 10.¹²⁸

Under the pediatric labeling regulations, the Agency defines “pediatric population(s)” and “pediatric patient(s)” as the age group “from birth to 16 years, including age groups often called ... adolescents.”¹²⁹ Therefore, the population of menstruating females (*i.e.*, 10 or 12 and older) and the pediatric population (*i.e.*, up to 16) overlap by up to 6 years. Based on Danco’s labeling and marketing to the menstruating female population without any age restriction, pediatric use of this product was clearly contemplated. Because Mifeprex will be used by some number of adolescent girls who become pregnant, FDA should have required the Sponsor to produce safety and effectiveness data for the pediatric population.

3. FDA Should Have Required the Submission of Pediatric Study Data Prior to Approving Mifeprex.

Under its broad authority granted by the FD&C Act, not only may FDA require the submission of pediatric data as part of a product’s NDA, but the Agency *must* require such data when the product’s conditions of use warrant pediatric testing. However, the Agency approved

¹²⁶ 5 USC § 706(2)(A).

¹²⁷ Instead, the drug’s labeling contains one non-constructive statement in the “Precautions” section of the labeling: “Safety and effectiveness in pediatric patients have not been established.” Given the logical reading of the drug’s indication and the medical information on the age range of menstruation, this one sentence in a package insert of 15 pages is valueless.

¹²⁸ See *On the Teen Scene: A Balanced Look at the Menstrual Cycle*, FDA Consumer Magazine (Dec. 1993) (available at: <http://www.fda.gov/fdac/reprints/ots_mens.html>). In the U.S., the average age of the start of menopause is 51. See *Taking Charge of Menopause*, FDA Consumer Magazine (Nov.-Dec. 1999) (available at: <http://www.fda.gov/fdac/features/1999/699_meno.html>).

¹²⁹ 21 C.F.R. § 201.57(f)(9).

Mifeprex without requiring the Sponsor to submit pediatric data or, apparently, any review of the pertinent scientific literature. When approving Mifeprex based solely on the data submitted in the NDA (*i.e.*, studies conducted in an adult population), FDA made the unsupported assumption that younger females (*i.e.*, children and adolescents) would have the same physiological response to this product as adult females.¹³⁰ Specifically, the Sponsor cited FDA's conclusion that "the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those of the age of 18 ...," despite the Agency's concession that most of the available data are from women 18 years and older.¹³¹ Further, the Sponsor noted that FDA has not found any "biological reason to expect that menstruating females under age 18 to have a different physiological outcome with the regimen."¹³²

As stated in the Petition, however, FDA's conclusion misreads the science. To assume, without specific data, that the effects of a potent antiprogesterone and a powerful prostaglandin analogue in pregnant adults will be the same for adolescents who are still developing in their physiologic, anatomic, and reproductive functions, is medically unsound. The relevant scientific evidence suggests that an assumption *cannot* be made that the effectiveness or safety of Mifeprex for adolescent girls is the same as for fully-developed adult women. Therefore, FDA's decision to the contrary lacks a sound and justified scientific basis.

Moreover, the Agency decision disregards decades of its own medical judgment. In the past, FDA has said that drugs should be studied directly in the pediatric population because "the action and adverse actions of pharmaceutical agents will vary as absorption, distribution, metabolism, and excretion, and receptor sensitivity are altered by the changes associated with growth and development."¹³³ For Mifeprex, these factors were not directly studied in children.

Studying the subpopulation of adolescents is even more important, according to FDA. For example, "[t]he development of puberty and the known effects of sex hormones on drug metabolism warrant consideration in drug evaluation in the adolescent."¹³⁴ Other "special problems" arise from the intense concern with self-image, leading to increased use (both admitted and denied) of prescription and over-the-counter drugs, dietary supplements, and cosmetics for such purposes as altering physical growth and sexual development, regulating mood and behavior, and influencing physical appearance.¹³⁵ FDA did not require a review of these adolescent-specific considerations with respect to the Mifeprex Regimen.

¹³⁰ See Mifeprex Approval Memo at 7.

¹³¹ Opposition Comments at 15 (citing 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 28).

¹³² Opposition Comments at 15 (citing Mifeprex Approval Memo at 7).

¹³³ FDA Guidance for Industry, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children" (Sept. 1977), at 6 (hereafter, "Pediatric Study Guidance").

¹³⁴ Pediatric Study Guidance at 15.

¹³⁵ See Pediatric Study Guidance at 16-17.

In addition, FDA has said previously that a drug's safety profile may be different for adolescents because "medication may not be taken as prescribed. The adolescent frequently omits doses of medication, takes it at erratic intervals, and may take more than prescribed. Safety considerations should be addressed not only to the therapeutic dosage, but also to the consequences of suboptimal dosage and overdosage."¹³⁶ Given the two-drug-regimen and three-doctor-visit administration of the Mifeprex Regimen, a study of patient compliance issues in adolescents was warranted.

Conclusion

In summary, it is logical to conclude that Mifeprex is intended for use by a female population that, under the pertinent definitions adopted by FDA, includes pediatric females. Therefore, FDA should have required the submission of pediatric data with the NDA. Without any consideration of pediatric data, FDA's approval of Mifeprex is an abrogation of its fundamental duty to conduct the drug approval process in a way that protects and promotes the public health and safety. In so doing, the Agency acted in a way that was arbitrary, capricious, and contrary to law and its own regulations.

II. FDA Is Both Statutorily Empowered and Obligated to Grant an Administrative Stay of the Mifeprex NDA Approval.

The Sponsor's Opposition Comments contain three technical objections to the request for an administrative stay of the Mifeprex NDA approval.¹³⁷ First, the Sponsor alleges that an administrative stay is not the appropriate method by which FDA could withdraw the Mifeprex NDA. Second, the Sponsor alleges that the request is "untimely" because it was not filed within 30 days of the effective date for the Mifeprex NDA approval. Third, the Sponsor makes a general allegation that the Petitioners do not meet the criteria for an administrative stay under FDA's regulations. As described below, these allegations stem from an incorrect and overly restrictive reading of the Petitioners' request. Instead of answering the serious substantive issues raised in the Petition, the Sponsor has focused on the way in which the Petitioners framed their request for FDA action. Even more disconcerting, the Sponsor asks FDA to place administrative procedures above the Agency's statutory obligation to protect the public health.

A. FDA Has the Statutory Authority to Suspend the Mifeprex NDA Pending the Outcome of a Decision to Withdraw the Application.

The Petitioners' request for administrative stay of the Mifeprex NDA approval is equivalent to a request for FDA to use its authority under section 505(e) of the FD&C Act to "suspend the approval of [the] application immediately."¹³⁸ The FD&C Act states that an NDA may be "suspended" whenever FDA makes a finding of "imminent hazard to the public

¹³⁶ Pediatric Study Guidance at 15.

¹³⁷ See Opposition Comments at 16-24.

¹³⁸ 21 U.S.C. § 355(e); see also 21 C.F.R. § 314.150(a)(1).

health.”¹³⁹ In the Petition and in this Response, the Petitioners have provided extensive evidence that Mifeprex poses, under FDA’s definition, “a significant threat of danger to health, [and] creates a public health situation . . . that should be corrected immediately to prevent injury.”¹⁴⁰ Furthermore, an emergency or “crisis” situation is not required, but merely a “substantial likelihood that serious harm will be experienced during . . . any realistic projection of the administrative process.”¹⁴¹ In interpreting this definition, a court upheld an FDA decision similar to that which the Petitioners are requesting. Specifically, even though “respectable scientific authority [could] be found on both sides of this question”, and “much of the raw data used by the [Agency] in arriving at its conclusion had been available for some length of time,” these facts did not preclude FDA’s use of the data in finding an imminent hazard when “the magnitude of [the drug’s] risk was determined only after an extensive *re-evaluation of the data*.”¹⁴²

FDA’s authority is resolute and can be exercised immediately, notwithstanding any related issues regarding how the matter was initially raised (*e.g.*, a Citizen Petition), who exercised the authority (*e.g.*, HHS Secretary or FDA), and what actions follow it (*e.g.*, notice and hearing).¹⁴³ FDA should disregard the Sponsor’s attempt to redirect the Agency away from the substance of the Petition toward a focus on the administrative requirements of delegating authority, providing notice, and holding a hearing. Clearly, FDA’s suspension of the Mifeprex approval could occur during the pendency of any notice period or hearing which the Sponsor so forcefully claims to be entitled to under the FD&C Act, the APA and Constitutional due process provisions. Given the situation, the Petitioners are dismayed at the Sponsor’s insistence that its “property right to produce and market Mifeprex,”¹⁴⁴ outweighs any concern for the safety of the patients that the Sponsor is seeking to “treat.”

Furthermore, even if FDA finds that an imminent hazard does not exist in this case, FDA may still summarily withdraw approval of an NDA in certain circumstances. During its four-page discussion on notice and hearings, the Sponsor fails to mention that the FD&C Act’s “due notice and hearing” provision does not guarantee an NDA Sponsor a hearing, and also leaves FDA with discretion regarding the type of notice that is provided.¹⁴⁵ Rather, FDA may proceed by summary judgment to withdraw an NDA in certain circumstances – for example, when there

¹³⁹ *See id.*

¹⁴⁰ 21 C.F.R. § 2.5.

¹⁴¹ *Forsham v. Califano*, 442 F. Supp. 203, 208 (D.D.C. 1977) (citing *Environmental Defense Fund v. EPA*, 510 F.2d 1292, 1297 (D.C. Cir 1975)).

¹⁴² *Forsham v. Califano*, 442 F. Supp. 203, 209 (D.D.C. 1977) (emphasis added).

¹⁴³ *Forsham v. Califano*, 442 F. Supp. 203 (D.D.C. 1977) (on petition raised by a consumer health organization, the HHS Secretary referred the matter to FDA, which withdrew approval of a drug with notice but no formal hearing, based on a finding of imminent hazard to the public health).

¹⁴⁴ Opposition Comments at 18. When the Sponsor included misoprostol as part of the Mifeprex Regimen, it did not demonstrate any concern for the property rights of Searle over misoprostol.

¹⁴⁵ *See John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 518, 520 (D.C. Cir. 1988) (“It is well settled that this [notice and hearing] provision does not guarantee the applicant a hearing in all circumstances.” and “The requirements of ‘due notice’ must depend upon the context of the agency’s action.”); *Brandenfels v. Heckler*, 716 F.2d 553, 555 (9th Cir. 1983) (“The FDA is authorized to satisfy its own notice requirements by providing holders of new drug applications with either general or specific notice of opportunity for hearing.”).

is no genuine and substantial issue of fact, when the applicant does not meet the minimum regulatory requirements, or when it appears conclusively from the applicant's pleadings that the applicant cannot succeed.¹⁴⁶

The Petitioners' request for administrative stay contains ample evidence to support a finding in this case of imminent hazard or the requisite basis for summary withdrawal. Millions of women are being misled to believe that the Mifeprex Regimen is safe, while in actuality neither the data submitted in the original NDA nor the subsequent marketing history can support a safety profile that justifies the continued marketing of the drug product. There is simply no legal basis to assert that FDA lacks the authority to grant the requested remedy of a "stay" (*i.e.*, suspension) of the NDA pending resolution of a formal NDA withdrawal process.

B. The Request for Administrative Stay Was Timely Filed.

An NDA is not a "static" document. Rather, it is a "living" document that is constantly being supplemented, updated, and reviewed by FDA.¹⁴⁷ Therefore, FDA is constantly making a "decision" to allow an NDA approval to stand in light of new information that is submitted to the Agency. Likewise, a drug's safety and efficacy profile and risk/benefit profile also require constant re-analysis by FDA. For example, over time "newer" medical evidence comes to light and adverse reactions are recorded in the patient population. FDA's approval decisions on NDAs are not "stuck in time." Instead, "FDA has an obligation to judge a drug's effectiveness by contemporary scientific standards. If those standards change to the extent that it is questionable whether a drug can be regarded as having been shown to be effective, FDA may under the act appropriately review the drug's status."¹⁴⁸

FDA's regulations state that a stay of action must be filed within 30 days of the "date of the *decision involved*" unless FDA permits a later filing for "good cause."¹⁴⁹ In this instance, the "decision involved" is FDA's decision to uphold the Mifeprex NDA and to *not* suspend the approval despite the influx of new information. This decision is ongoing. The Petitioners are requesting that FDA "stay" that decision and suspend the NDA approval immediately in response to the imminent hazard presented by the Mifeprex Regimen.

¹⁴⁶ See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 620-1 (1973) (withdrawing approval of NDA without a hearing based on lack of evidence negating "new drug" status); *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 518 (D.C. Cir. 1988) (withdrawing approval of NDA without a hearing based on failure to comply with current good manufacturing practices); *Cooper Laboratories, Inc. v. FDA*, 501 F.2d 772, 780 (D.C. Cir. 1974) (withdrawing approval of NDA without a hearing based on insufficient evidence of efficacy).

¹⁴⁷ See, *e.g.*, 21 C.F.R. §§ 314.70, 314.72, 314.80, 314.81. At the very least, the Sponsor of the Mifeprex NDA is required to submit an annual report to FDA each year. 21 C.F.R. § 314.81(b)(2). The Sponsor's misdirection on this matter is revealed by the fact that, under their interpretation of the "30 days" filing requirement, the Petitioners could "cure" the alleged timeliness defect by merely submitting the Petition within 30 days of any Mifeprex NDA Supplement or Annual Report.

¹⁴⁸ 50 Fed. Reg. 7452, 7488 (Feb. 22, 1985) (FDA's rejection of an industry suggestion, on withdrawal of approval of an application under 21 C.F.R. § 314.150, that FDA's conclusion concerning a drug product "should remain unchanged even if FDA later adopted new standards").

¹⁴⁹ 21 C.F.R. § 10.35(b) (emphasis added).

Even if the request were considered to be “untimely” from a technical perspective, FDA should nevertheless still grant the requested stay pursuant to either (1) the Agency’s “imminent hazard” authority under section 505(e), which contains no time limitation; or (2) the “good cause” exception of 21 C.F.R. § 10.35(b). In fact, the “imminent hazard” authority and the “good cause” exception were included in the statute and regulations for the very reasons outlined in the Petitioners’ request. Namely, these provisions allow FDA to move quickly to protect the public from unsafe drug products without being slowed by overly technical readings of the regulations. Additionally, if FDA deemed the request to be untimely filed, the Agency still may stay its action on the NDA on its own initiative *at any time*. In other words, if FDA determines that the Petition’s underlying request has merit, FDA may suspend approval and/or initiate withdrawal proceedings independent of the Petitioners’ request.

C. The Petitioners Comply with the Spirit and Letter of the Requirements for an Administrative Stay.

As supported by the original submission, the Petitioners’ request for an administrative stay meets all of the requirements of 21 C.F.R. § 10.35(e). In particular, the Petitioners have demonstrated irreparable harm to American women and an overwhelming public policy reason for removing the Mifeprex drug product from the market. The Petitioners’ request is clearly not frivolous, and is being pursued in good faith. In response, the Sponsor has raised minor technical challenges that obfuscate and mischaracterize the issues raised by the Petitioners. Despite the evidence contained in the Petition concerning the harm that Mifeprex is inflicting on American women, and the Petitioners’ direct interest as their physicians in speaking for these women, the Sponsor has alleged that there is insufficient injury to justify an administrative stay. Specifically, the Sponsor argued that the Petitioners are not the *actual* injured party.¹⁵⁰ Yet, that response is a mischaracterization of the Petitioners’ request. The Petition clearly stated that the Petitioners were seeking Agency action to prevent further injury to women seeking to terminate their pregnancies.¹⁵¹ The evidence submitted in the Petition and in this submission unequivocally demonstrates that women are being harmed by this drug product. In light of this fact, FDA is obliged to investigate whether the Mifeprex NDA approval should be suspended and ultimately withdrawn.

¹⁵⁰ See Opposition Comments at 21-22.

¹⁵¹ Just as the Petitioners have with their Petition, patient advocacy groups routinely utilize the Citizen Petition process to request that FDA overturn its safety and effectiveness decision for drug products and, ultimately, withdraw them from the market. See Letter to FDA from AIDS Healthcare Foundation, August 19, 2003 (Docket number not assigned), requesting market removal of Trizivir (abacavir sulfate/lamivudine/zidovudine) due to poor efficacy results in post-approval clinical studies letter; Docket No. 02P-1778, Citizen Petition from Public Citizen and Arizona Arthritis Center, March 28, 2002, requesting market removal of Arava (leflunomide) due to patient deaths and severe liver failure; Docket No. 02P-0120, Citizen Petition from Public Citizen, March 19, 2002, requesting market removal of Meridia (sibutramine) due to patient deaths related to cardiovascular adverse effects. Many of these Citizen Petitions are ultimately successful. See *e.g.*, Rezulin (troglitazone), banned March 2000 after a July 1998 Petition (Docket No. 98-0622); and Lotronex (alosetron HCl), banned November 2000 after an August 2000 Petition (Docket No. 00P-1499).

III. Conclusion.

For the foregoing reasons, the Petitioners respectfully request that FDA immediately suspend the approval of the NDA for Mifeprex and enter an administrative stay to halt any further distribution and marketing of Mifeprex until final Agency action is taken to withdraw the NDA approval for Mifeprex. For copies of any of the reference materials cited herein, please contact the undersigned.

Respectfully submitted,

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