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/CP1

The Population Council, Inc. and Danco Laboratories, LLC, through counsel, submit these comments in opposition to the Citizen Petition and Request for Administrative Stay ("Petition") filed on August 20, 2002 by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America ("Petitioners"). Petitioners seek an "immediate stay" of the approval of Mifeprex® (mifepristone) pending final action on the Petition, thereby halting all distribution and marketing of the drug, and also request that the Food and Drug Administration ("FDA") revoke its approval of Mifeprex.

The Population Council, Inc. ("the Council") is a non-profit organization which seeks to improve the well-being and reproductive health of current and future generations around the world. Its activities include developing drugs for the improvement of reproductive health. In order to make the drugs it develops actually available to patients and consumers, it licenses them to companies which manufacture and distribute them in the marketplace. Danco Laboratories, LLC ("Danco"), a women's health pharmaceutical company, is the pharmaceutical company which the Council has licensed to manufacture and market mifepristone. The Population Council was the original sponsor of the Mifeprex New Drug Application ("NDA"). Effective October 31, 2002, ownership of the NDA was transferred from the Council to Danco. The Council and Danco are sometimes referred to herein as the sponsors of the NDA.

The Petition must be denied for the following reasons.

First, FDA's approval of Mifeprex was proper, indeed required, because the drug was shown to be safe and effective. As FDA said at the time, "The approval of mifepristone is the

result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug. The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency." U.S. Dep't of Health and Human Services, Press Release P00-19, "FDA Approves Mifepristone For the Termination of Early Pregnancy" (Sept. 28, 2000), available at www.fda.gov/bbs/topics/news/NEW00737.html. Nothing that has happened in the more than 2 years since Mifeprex was approved requires or allows FDA to change its conclusion that the drug is safe and effective. Thus, whether the Petition is understood as a request for FDA to withdraw the Mifeprex NDA immediately or to initiate withdrawal proceedings, it must be denied because FDA cannot satisfy the requisites for beginning such a proceeding, much less meet the requirements for withdrawing the NDA for Mifeprex.[1]

Second, the relief petitioners seek - the immediate cessation of distribution and marketing of Mifeprex - is tantamount to withdrawal of the NDA for Mifeprex. Under the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and FDA's implementing regulations, the Administrative Procedure Act ("APA"), and the Due Process Clause of the Constitution, an NDA can be withdrawn only after FDA has given the sponsor notice and an opportunity for a hearing and has met the statutory substantive criteria for withdrawal. These substantive and procedural requirements cannot be bypassed by means of a stay or a response to a Citizen Petition.

Third, even if FDA could properly stay an NDA, Petitioners have not met the criteria for a stay imposed by FDA's regulations.

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1. Petitioners also request a full FDA audit of the Mifeprex clinical studies. Petition at 1. Because FDA has already audited representative sites, the Council and Danco believe that expending FDA resources on further audits is unnecessary.

I. FDA Properly Approved The Mifeprex NDA and Nothing That Has Happened Since Allows or Requires It to Revoke the Approval

Petitioners argue that approval of Mifeprex was based on agency actions that are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." Petition at 4. Petitioners' assertion that FDA approval was unlawful is incorrect. Their challenges to FDA's actions in the eight respects summarized on pages 4-7 of the Petition and discussed in more detail later in the Petition are unfounded, both legally and factually, as are other challenges scattered throughout the Petition. The rigor, completeness, and regularity of FDA's review is reflected in the public record supporting the September 28, 2000, approval. See, e.g., FDA, CDER, Mifepristone Information, available at www.fda.gov/cder/drug/infopage/mifepristone/default.htm (last visited Mar. 11, 2003); FDA, CDER, Mifepristone Approval Package, available at www.fda.gov/cder/foi/nda/2000/20687_mifepristone.htm (last visited Mar. 11, 2003). Mifeprex was and is safe and effective and appropriately labeled. That is why FDA approved it, and that is why FDA approval remains mandatory.

A. FDA Believes It Has Authority to Regulate Mifeprex Pursuant to Subpart H, but Even if That View Is Erroneous, Its Approval of Mifeprex Was Lawful

The Petition argues that FDA should not have approved mifepristone under Subpart H because it is not a drug for the treatment of a serious or life threatening illness. Petition at 18-23. It then concludes that because Subpart H should not have been an option available to FDA, the drug should not have been approved at all. Id. at 23. The question of whether FDA should or could properly have invoked Subpart H certainly is arguable – indeed the Council and Danco opposed it. But Petitioners draw the wrong conclusion.

The restrictions FDA imposed under Subpart H could as well have been imposed (and enforced) under Section 505 itself, without reference to Subpart H. In citing Section 505(d) as authority for its Subpart H regulations, FDA has itself claimed authority to impose restrictions on

distribution and labeling under NDAs. In accordance with that authority, FDA imposed distribution restrictions by means of an NDA in the case of Clozaril (clozapine), New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, 57 Fed. Reg. 13234, 13236 (proposed Apr. 15, 1992) (to be codified at 21 C.F.R. §§ 314.500-50), and also imposed restrictions on Accutane by means of an NDA. Letter from Frank E. Young, Commissioner of Food and Drugs, to William B. Schultz, Public Citizen Litigation Group at 2, FDA Docket No. 88P-0191 (May 2, 1989). See also Petition of Public Citizen to Declare Accutane an Imminent Hazard and to Immediately Approve Limitations on its Distribution at 10-11, FDA Docket No. 88P-0191 (May 17, 1988) (FDA has authority to impose conditions, including limitations on distribution, under section 505, citing, inter alia, Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16503, 16504 (proposed Aug. 15, 1972) (to be codified at 21 C.F.R. pt. 130)). Thus, FDA has at least one and, in FDA's view, two sources of authority for imposing (and enforcing) restrictions with respect to Mifeprex – Section 505(d) itself and Subpart H, a regulation issued pursuant to Section 505(d). Only Section 505(d) was necessary to the approval, so even if Subpart H fails, the approval was lawful. Accordingly, there is no basis for withdrawing FDA's approval of the Mifeprex NDA on this ground.

It is important to note that Petitioners' emphasis on their contention that the Council and Danco refused to cooperate with FDA in considering and devising labeling and distribution plans that would contribute to safe use of the drug and had to be coerced into grudging compliance is misplaced. It was the Council (not FDA) which originally proposed a restricted distribution plan in 1996. See Beverly Winikoff, M.D., M.P.H., Program Director for Reproductive Health Programs, Population Council, Presentation at Meeting of Reproductive Health Drugs Advisory Committee at 80-81 (July 19, 1996), available at www.fda.gov/ohrms/dockets/ac/96/transcpt/3198t_1_a.pdf . In January 2000, Danco submitted a "comprehensive distribution plan" which embodied "appropriate distribution

controls," Letter from The Danco Group to FDA at 1 (Jan. 12, 2000), available at www.fda.gov/cder/archives/mifepristone/MIF000501.pdf at MIF000525-31 (hereinafter "Danco Letter");[2] a revised version of the distribution plan was submitted in March 2000. In addition, the sponsors proposed a package of materials to provide detailed information for prescribers and for women considering abortion, including the Patient Agreement, the Patient Information Sheet (which became the Medication Guide), and the Prescriber's Agreement. FDA, the Council, and Danco discussed extensively and intensively the details of how the distribution plan should work, what kinds of patient and physician information would be most helpful, and many other related issues. The decisions FDA reached in these regards were ultimately incorporated into its approval of Mifeprex. The result is a distribution plan and a package of informative and useful materials for physicians and patients which enhance this already safe drug in actual use.

Equally important, the sponsors did not oppose making the restrictions enforceable. To the contrary, although they objected to the imposition of Subpart H, they repeatedly told FDA that Subpart H was unnecessary because FDA had authority under Section 505 itself to impose enforceable distribution requirements and enforceable commitments to distribute labeling such as the Patient Agreement, the Patient Information Sheets, and the Prescriber's Agreement. Thus, as the Council told FDA in September, 2000, if FDA were to incorporate the Council's and Danco's commitments into the approval of the NDA, the Council and Danco would:

> be bound not only by their freely given commitment but also by law to carry out the distribution of mifepristone in accordance with the system presented in the NDA and approved by FDA . . . The Population Council and Danco will also be bound by law not to change the distribution system without changing the labeling, and they cannot lawfully change the labeling without an approved

2. Unless otherwise noted, FDA documents such as letters from Danco and the Population Council which, because they are posted on FDA's website, are routinely available to the public, are cited in this document and incorporated herein by reference but are not attached, pursuant to 21 C.F.R. § 10.20(c).

> NDA supplement. Thus, the NDA approval process wraps us up every bit as tightly as Subpart H.

Letter from Sandra P. Arnold, Vice-President of Corporate Affairs, Population Council, to FDA at 4 (Sept. 6, 2000), available at www.fda.gov/cder/archives/mifepristone/MIF001301.pdf at MIF001333-49 (emphasis in original) (hereinafter "September Arnold Letter").

In short, although there was debate about Subpart H, the result would have been the same whether FDA utilized Subpart H or only Section 505 itself: restrictions FDA thought necessary to the approval would have been imposed and would have been enforceable. Having chosen Subpart H, FDA will presumably continue to defend its choice. Though continuing to oppose FDA's choice, Danco and the Council will continue, as they always intended, to honor their commitments to carry out the program of restrictions imposed in the approval letter.

B. Clinical Trials Demonstrate That Mifeprex is Effective

Petitioners argue that the clinical trials in which Mifeprex was evaluated for efficacy do not meet the statutory and regulatory standards for such trials on several grounds. They assert that the trials do not provide clinically significant evidence of efficacy, that they were not adequate and well-controlled, that there were not enough studies, and that the efficacy requirements of Subpart H were not met. Petition at 5, 22-41. In fact, the clinical trials of Mifeprex were clinically and legally adequate to demonstrate efficacy, and did so.

Mifeprex was extensively studied for efficacy. The NDA contained three pivotal (major) studies, two conducted in France and one conducted in the United States, as well as numerous other studies conducted throughout the world. In these major studies, 92-95% of the 2508 women evaluated for efficacy had complete abortions (defined as the complete expulsion of products of conception without the need for surgical intervention). FDA Office Memorandum to NDA 20-687 MIFEPREX (mifepristone) at 1 (Sept. 28, 2000), available at

www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (hereinafter "FDA Approval Memo"). By comparison, the rate of spontaneous abortion in the first trimester is assumed to be about 10%. WILLIAMS OBSTETRICS 581 (F. Gary Cunningham et al. eds., 20th ed. 1997). The French data were reviewed by an FDA Advisory Committee, which agreed by a vote of 6-2 that the data demonstrated efficacy; after FDA provided the United States data to the Committee, no member of the Committee advised FDA that her or his view of efficacy was changed by the United States data. FDA Approval Memo at 1. The data clearly demonstrate efficacy, as FDA concluded. Id.

At the heart of Petitioners' challenge to the clinical trials is the erroneous assumption that historically controlled trials cannot be adequate and well-controlled. Yet as Petitioners themselves recognize, Petition at 35, FDA's regulations explicitly include historically controlled trials in the category of trials that can constitute substantial evidence. 21 C.F.R. § 314.126(b)(v). They are appropriate when the natural history of the condition is well-known and well-documented, and when the effects of the drug are self-evident. These criteria are satisfied here. Similarly, FDA's E10 Guidance provides that historical (externally controlled) trials are persuasive when, inter alia, the study endpoint is objective and outcome on treatment is markedly different from that of the historical controls. FDA, CDER/CBER, Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials at 28 (May 2001), see Notice of Availability; International Conference on Harmonisation; Choice of Control Group and Related Issues in Clinical Trials, 66 Fed. Reg. 24390 (May 14, 2001). The Guidance also states that comparing a patient to her baseline status is reasonable when the effect of the drug is dramatic, occurs rapidly following treatment, and is unlikely to have occurred spontaneously. Id. at 26. The Guidance's criteria, too, are satisfied.

The results of the studies were certainly clinically significant: 92-95% of the women who participated in the clinical trials, like women who are now using the approved drug, experienced the clinical effect they sought: medical abortion.

Petitioners discuss at some length FDA's requirements for allowing approval of NDAs based on one rather than two or more studies. It is not clear why they raise this issue, because FDA's approval of Mifeprex is supported by three pivotal studies. FDA Approval Memo at 1. Any one of the pivotal studies could alone have supported approval under the applicable standards, but the presence of three moots the point.

Although Petitioners argue pointedly in other sections of their Petition that Subpart H was inappropriately utilized for Mifeprex, they nevertheless also assert that Subpart H should be used to evaluate the efficacy data in the Mifeprex NDA. According to Petitioners, FDA should have required the sponsors to compare Mifeprex to surgical abortion in clinical trials as a means of demonstrating the "meaningful therapeutic benefit over existing therapies" required by Subpart H. 21 C.F.R. § 314.500. The quoted language is not a description of required clinical trials. Appearing in the Scope section of the regulations, it is merely a description of the threshold FDA uses to decided whether to use Subpart H for certain drugs, a threshold Mifeprex exceeds. Mifeprex has several benefits over existing therapies, including the avoidance of a surgical procedure, FDA Approval Memo at 1, and usefulness at an earlier stage of gestation. FDA, CDER, Medical Review of Application 20-687 (Mifepristone) (Part 1) at 27, available at www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (hereinafter "FDA Medical Review"). These benefits are readily evaluated without resort to clinical trials.

In any case, nothing in Subpart H specifies that the determination of meaningful therapeutic benefit must be based on comparative clinical trials with, e.g., an active control or

treatment/no treatment.[3] In fact, the first two parenthetical examples provided in the Scope section (ability to treat patients unresponsive to or intolerant of available therapy) essentially preclude comparative trials because the existing therapy does not work in the patients in question. Moreover, FDA routinely approves drugs under Subpart H on the basis of study designs that do not compare the Subpart H drug directly to existing therapy. See, e.g., FDA, CDER, Supervisory Review of NDA 20-785 (Thalomid) (July 7, 1998), available at www.fda.gov/cder/news/thalinfo/20785medr.htm. It would be inappropriate to apply to Mifeprex standards different from those applied to other drugs. Bracco Diagnostic, Inc. v. Shalala, 963 F. Supp. 20, 27-28 (D.D.C. 1997).[4]

C. Inclusion of Misoprostol in the Mifeprex Regimen Was Not Unlawful.

Petitioners attack the inclusion of misoprostol in the approved Mifeprex regimen and its discussion in the Mifeprex labeling, and argue that its inclusion puts both FDA and Danco in the position of unlawfully promoting misoprostol off-label. Petitioners omit to state 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. In the oncology area, for example, the list includes Xeloda (capecitabine) in combination with Taxotere (docetaxel). In the diabetes area, the list includes Actos (pioglitazone HCl) in combination with a sulfonylurea, metformin, or insulin. In the HIV/AIDS area, the list includes Viread (tenofovir disproxil fumarate) in combination with other antiretroviral agents. In the duodenal

3. Cf. Defendant's Reply Memorandum in Support of Its Motion for Summary Judgment at 8 n.4, Judicial Watch, Inc. v. FDA, No. 00-02973 (RJL) (D.D.C. filed Dec. 12, 2000) (in case of Mifeprex, no requirement of two blinded comparator controlled trials).

4. It should also be noted that the clinical trials of mifepristone were designed and carried out well before FDA decided to apply Subpart H to the drug. Even if the agency were to decide prospectively to require the comparative trials urged by Petitioners as a general matter, it cannot retroactively apply that standard to Mifeprex.

ulcer/helicobacter pylori area, the list includes Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin.

No one has ever alleged that this common practice makes the previously approved drug an unlawful new drug[5] or puts either FDA or the sponsor of the later-approved drug in the position of "promoting" off-label use of the previously approved drug. Thus, if Mifeprex (and misoprostol) are treated like other drugs, then FDA's utilization of a practice it uses routinely with other drugs must also be permissible here.

D. Mifeprex is Safe

Petitioners' challenge to the safety of Mifeprex contains two main components: 1. FDA's approval did not incorporate every restriction or limitation that had ever been considered or proposed by anyone during the review process, and 2. FDA did not require that certain elements of the protocol used in the clinical trials of Mifeprex be carried over to the labeling of the approved product. Neither is required by law and neither is required for safe use of Mifeprex. What is required, and what FDA did, was to rest its approval on the conclusion that with the restrictions imposed the drug is safe for use. The track record of Mifeprex in actual use shows that FDA's decisions were correct. Hausknecht RU. Mifepristone and Misoprostol for Early Medical Abortion: First Eighteen Months' Experience in the United States. Contraception. In press June 2003 ("Initial United States experience with mifepristone and misoprostol for early medical abortion confirmed the safety" of their use).

One aspect of Petitioners' argument has been discussed above: although it is correct that the sponsors of the Mifeprex NDA opposed imposition of Subpart H, they did not oppose,

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5. "Newness" of a drug can arise not only from new indications but also from such new conditions of use as new comcomitant medications and other changes in dosage and administration. 21 C.F.R. § 310.3(h).

and indeed themselves proposed, many of the same restrictions under authority of Section 505 of the statute. For example, the sponsors proposed the concept of restricted distribution and the specific distribution plan ultimately adopted. They also proposed the Prescriber's Agreement, Patient Agreement, and Patient Information Sheet (which later became the Medication Guide), which contribute significantly to safe use of the drug. Supra at 4.

To be sure, the sponsors did not agree that every restriction proposed along the way would actually contribute to the safety of the product, and they argued vigorously, and appropriately, against restrictions they thought would add to the cost or red tape of obtaining Mifeprex without any corresponding benefit in safety. See, e.g., September Arnold Letter; Letter from Sandra P. Arnold to FDA (June 23, 2000), available at www.fda.gov/cder/archives/mifepristone/MIF001401.pdf at MIF001438-46 (hereinafter "June Arnold Letter"). That there was discussion, negotiation, give and take, debate, even on occasion disputes, between FDA and the sponsors is characteristic of the review process for many drugs. In the end, FDA must make its decisions under the statutory criteria, and does not approve drugs unless it concludes that the statutory criteria are satisfied, as they were here.[6]

That FDA chose not to incorporate every aspect of the clinical trials in the labeling was not inappropriate, nor is it uncommon. In clinical trials, standardization is useful, even necessary, to allow evaluation of the drug. When the issue is treating patients, however, rather than evaluating drugs, such standardization is often unnecessary and may even be counter-productive. Petitioners object, for example, to FDA's decision not to require

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6. Petitioners argue, in effect, that the views of FDA staff who proposed certain restrictions should be heeded in preference to the views of the final decisionmaker as reflected in the FDA Approval Memorandum and the FDA Approval Letter. Deference is owed not to every individual employee, but to the final decisionmaker. Serono Laboratories, Inc. v. Shalala, 158 F.3d 1313, 1321 (D.C. Cir. 1988). Were it otherwise, each FDA employee would have the power to veto decisions made by agency management. Id.

evaluation of gestational age by ultrasound, as was done in the U.S. clinical trial. Petition at 57-61. FDA properly concluded that this was unnecessary:

> The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgment of the physician.

FDA Approval Memo at 5. See also June Arnold letter at 5.

Similarly, there was no need for FDA to insist that every physician who prescribes Mifeprex for her or his patients have admitting privileges at an emergency facility or have the ability to perform surgical abortion if necessary. As the sponsors explained to FDA:

> Specialization is a fact of life in modern American medical practice, and it is absolutely routine for physicians to refer patients to one or more other physicians for various aspects of their care...There is no reason at all for mifepristone to be one of the very few exceptions to these common practices...
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> There is nothing about the care... attendant [to] prescribing....mifepristone which [requires that it be treated differently than pregnancy itself]. To the contrary,... the emergency/surgical care for incomplete abortion and heavy bleeding following mifepristone is literally identical to the emergency/surgical care for miscarriage, i.e., spontaneous abortion. Because miscarriages occur in some 15-20% of pregnancies, the treatment protocols for the necessary emergency and surgical care...are well established. Obstetrician/gynecologists, family practitioners, and others who do surgery...treat such patients themselves, and practitioners who do not do surgery...refer them.

June Arnold Letter at 6 and Letter from Sandra P. Arnold to FDA at 6 (July 27, 2000), available at www.fda.gov/cder/archives/mifepristone/MF001301.pdf at MIF001373-81. FDA agreed:

> [P]atients [can] get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed.

FDA Approval Memo at 5. The agency concluded that providing information in the labeling to guide physicians in caring for their patients was appropriate. Id.

Petitioners argue that the adverse events reported since the Mifeprex approval demonstrate that the drug should not be approved. These adverse events reports have been evaluated by FDA, which concluded that none cast any doubt on the agency's determination that the drug is safe. FDA, CDER, Mifepristone Questions and Answers (Apr. 17, 2002), available at www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm (hereinafter "FDA Dear Doctor Mifeprex Q & A").

The serious adverse events reported include a few cases of ruptured ectopic pregnancies and serious systemic bacterial infections and a single case of a heart attack. But FDA has not found any causal connection between these events and the use of Mifeprex and misoprostol. Id. at No. 1 ("At this time, it is unknown whether there is a causal relationship between any of these events and the use of Mifeprex and misoprostol.").

The issue of ectopic pregnancy is not related to abortions, whether surgical or medical. Ectopic pregnancies, though rare, do occur. As FDA has noted, an ectopic pregnancy "happens before the woman knows she is pregnant and is not caused by the mifepristone regimen." Id. at No. 4. Physicians sometimes fail to diagnose an ectopic pregnancy correctly and some ectopic pregnancies do rupture. But this could occur with a patient seeking to carry to term or one seeking either a medical or surgical abortion. Danco has reminded physicians in a "Dear Health Care Provider" letter about the need "to be mindful of the possibility of an ectopic pregnancy throughout the treatment period and have a plan for its management." Letter from Danco Laboratories to Health Care Providers at 1 (Apr. 19, 2002), available at www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf (hereinafter "Dear Health Care Provider Letter").

Severe systemic bacterial infection can occur in the context of menstruation, childbirth, and abortion (whether spontaneous, surgical, or medical). E.g., Prosser BJ, Horton J. A Rare Case of Serretia Sepsis and Spontaneous Abortion (letter). N Engl J Med 2003; 348: 668-9. It was for that reason that Danco was willing to remind physicians of the need to be alert to the possibility of infection in the context of abortion generally, including medical abortion, to assist them in caring for their patients. See Dear Health Care Provider Letter. But infection is no more likely to occur in medical abortion than in spontaneous or surgical abortion and there is no reason to believe that infection is any more likely to occur with mifepristone and misoprostol than with other drugs.

The sponsors could ascertain no temporal or biological explanation for the association of the reported myocardial infarction with Mifeprex, and FDA agreed that "it cannot be known whether the drugs [mifepristone, misoprostol] contributed to the event." FDA Dear Doctor Mifeprex Q & A at No. 4.

E. The Sponsors Are Meeting Their Obligations with Respect to the Restrictions

Physicians prescribing Mifeprex "off-label" does not mean the sponsors are not meeting their obligations. The Prescriber's Agreement asks a physician to agree to meet the guidelines in the Agreement, and the guidelines, inter alia, ask physicians to provide patients with the Medication Guide and other required labeling and to report serious adverse events. Petitioners provide no information that physicians are not doing so. The guidelines do not state any specific dose or regimen for prescribing Mifeprex, and physicians who prescribe Mifeprex, like those who prescribe any other FDA-approved drug, may, as part of their practice of medicine, choose to prescribe the drug based on, e.g., published literature and other authoritative sources of information. See FDA Dear Doctor Mifeprex Q & A at No. 12-13. "Because physicians exercise their judgment in prescribing what they feel is best for the

patient, they may decide to use an 'off-label' regimen, rather than the approved regimen." Id. at No. 9.

F. No Pediatric Testing was Required.

Petitioners contend that FDA's failure to require pediatric testing under 21 C.F.R. § 314.55 invalidated the approval of Mifeprex. Petition at 77-83. Under the pediatric testing rule, pediatric testing was not required if FDA concluded that "the course of the [condition] and the effects of the drug are sufficiently similar in adults and pediatric patients" so that effectiveness could be extrapolated from studies in adults. 21 C.F.R. § 314.55(a). See also id. at § 314.55(c) (providing additional grounds for waiver). FDA explicitly and properly applied these criteria in waiving the rule. The FDA Medical Review notes that most of the available data are from women 18 years or older, but states 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..." FDA Medical Review at 28. The FDA Approval Memorandum reached the same conclusion: "FDA agrees that there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen." FDA Approval Memo at 7. In any event, because FDA is now enjoined from enforcing the rule, Ass'n of Am. Physicians and Surgeons v. FDA, 226 F. Supp. 204 (D.D.C. 2002), this issue is moot.

G. The Phase IV Study Commitments FDA Required Were Appropriate

Petitioners assert that FDA improperly "narrowed" the scope of the Phase IV studies it required of the sponsors. Petition at 6-7, 85. The kinds of studies required were changed, but not for any improper reason or with any improper result. Rather, the changes in the kinds of studies reflected changes to the distribution system and labeling and allowed the sponsors to focus on issues of greatest interest in light of the final approval. See FDA Approval Memo at

7. Also, several of the studies were combined, so that although the number of studies is smaller, the range of topics is not. For example, the cohort-based study comparing safety outcomes of patients treated by physicians with surgical intervention skills with those treated by physicians who refer their patients for surgical interventions will also look at questions related to age, smoking, and follow up on day 14, and will check signed patient agreements, topics which were previously to be explored in separate studies. Combining topics in this fashion will be more efficient.

II. FDA Cannot Use Either the Stay Provisions of 21 C.F.R. §10.35 or the Citizen Petition Provisions of 21 C.F.R. §10.30 as Alternatives to § 505(e) of the Food, Drug, and Cosmetic Act

Petitioners explicitly request revocation, i.e., withdrawal, of the Mifeprex NDA and also request a stay of the Mifeprex approval, "thereby halting all distribution and marketing of the drug" pending final action on the Petition. Petition at 2. FDA cannot lawfully force a cessation of marketing and distribution of a drug with an approved NDA by means of a stay or by granting a Citizen Petition. Because FDA has approved the NDA for Mifeprex under Section 505 of the FDCA, Letter from FDA to Sandra P. Arnold (Sept. 28, 2000), available at www.fda/gov/cder/foi/appletter/2000/20687appltr.pdf, the drug can be lawfully distributed and marketed pursuant to Section 505(a) unless and until the NDA is withdrawn pursuant to Section 505(e) of the Act.

The protections afforded sponsors under the Act are reinforced by the APA, with which FDA must also comply. Air N. Am. v. Dep't. of Transp., 937 F.2d 1427 (9th Cir. 1991). Under the APA, an agency cannot revoke an already-approved license without first providing notice and an opportunity to demonstrate compliance with all lawful requirements. Finally, the Due Process Clause of the Constitution also requires notice and the opportunity for a hearing before an NDA can be withdrawn or revoked. Neither a "stay" nor an agency response to a

Citizen Petition can be used to bypass the procedural and substantive protections afforded to sponsors by Section 505(e) and FDA's implementing regulations, the APA, and the Constitution.

FDA is not free simply to revoke its approval, as Petitioners request. See Motor Vehicle Mfrs Ass'n v. State Farm Mut. Auto. Ins., 463 U.S. 29 (1983). To reverse course, an agency must supply a reasoned analysis based on the relevant data. Id. See also Pearson v. Shalala, 164 F.3d 650, 660 (D.C. Cir. 1999). Section 505(e) of the FDCA explicitly states both the procedures and the standards that FDA must use to change its course with respect to the Mifeprex NDA.

First, Section 505(e) requires FDA to provide "due notice" to the applicant. See also 21 C.F.R § 314.200. The notice must give the applicant a fair opportunity to address any deficiencies perceived by FDA. Brandenfels v. Heckler, 716 F.2d 553, 555 (9th Cir. 1983). Under Section 505(e) and 21 C.F.R. § 314.200, the applicant is entitled to request a hearing on a proposed withdrawal and FDA must grant the hearing to resolve disputed issues. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 622-23 (1973); E.R. Squibb & Sons, Inc. v. Weinberger, 483 F.2d 1382, 1384 (3d Cir. 1973).[7]

Second, Section 505(e) requires FDA to make specific substantive findings before it can withdraw an approval. Withdrawal decisions must be based on the following: (1) that clinical or other experience, tests or other scientific data show that the drug is unsafe for use under the

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7. Under very rare circumstances, marketing of an approved drug can be halted before the sponsor receives the notice and opportunity for a hearing required by Section 505(e), but only if the Secretary of Health and Human Services finds that a product presents an "imminent hazard to the public health." 21 U.S.C. § 355(e). Even under these exigent circumstances, the Secretary (not the Commissioner of Food and Drugs) may only suspend an approval (not stay it indefinitely or revoke it) while the Commissioner of Food and Drugs provides on an expedited basis the notice and opportunity for a hearing required by Section 505(e). Id. Petitioners have not even attempted to meet the very high burden of showing that Mifeprex presents an imminent hazard, nor could they have succeeded had they tried.

conditions of use upon the basis of which the application was approved; or (2) that new evidence of clinical experience, not contained in such application or not available until after such application was approved, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available when the application was approved, shows that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information, evaluated together with the evidence available when the application was approved, that there is lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. 21 U.S.C. § 355(e).[8] These findings must be supported by substantial evidence. Warner-Lambert Co. v. Heckler, 787 F.2d. 147, 151 (3d Cir. 1986).

Section 505(e) unambiguously delineates the process that must precede FDA's decision to withdraw its approval and the findings that FDA must make before it can do so. FDA may not ignore "the unambiguous command of a statute." Torpharm Inc. v. Shalala, 1997 U.S. Dist. Lexis 21983 (D.D.C. Sept. 15, 1997).

In addition to the provisions of Section 505(e), FDA also must comply with the APA. The APA requires FDA to provide notice and the opportunity for a hearing prior to the withdrawal, suspension, revocation or annulment of a license. See 5 U.S.C. § 558(c).

The rights recognized in the FDCA and the APA reflect constitutional due process protections. As the holder of an NDA, Danco has a property right to produce and market Mifeprex. See, e.g., Barry v. Barchi, 443 U.S. 55 (1979); Richardson v. Town of Eastover, 922 F.2d 1152, 1156 (4th Cir. 1991) ("A license issued by the state which can be suspended or revoked only upon a showing of cause creates a property interest protected by the Fourteenth

8. The statute also includes other grounds for withdrawal not placed at issue by Petitioners, such as untimely filing of patent information. See id.

Amendment."). This property right is protected by the Due Process Clause, which guarantees that it cannot be modified, suspended, revoked or withdrawn without the opportunity to be heard at a meaningful time and in a meaningful manner. See, e.g., Mathews v. Eldridge, 424 U.S. 319 (1976); Bell v. Burson, 402 U.S. 535, 539 (1971); Hornsby v. Allen, 326 F.2d 605, 608 (5th Cir. 1964).

Minimum due process requirements include notice of the government's grounds and opportunity for a hearing. Mathews v. Eldridge, 424 U.S. at 333; Bowman Transp., Inc. v. Arkansas-Best Freight Sys, Inc., 419 U.S. 281, 288 n.4 (1974) (due process entitles a party to know issues on which decision will turn and to be apprised of the factual material on which the agency relies for decision so he may rebut it); Goldberg v. Kelly, 397 U.S. 254, 264-70 (due process requires government to disclose evidence on which it relies in action); Hess & Clark v. FDA, 495 F.2d 975, 983 (D.C. Cir. 1974) (agency may not validly deny a hearing unless it provides notice which "specifies the nature of the facts and evidence on which the agency proposes to take action;" evidence must constitute "a prima facie case"). Suspension or revocation through the Citizen Petition or stay procedures would violate these due process rights.

FDA's Citizen Petition and stay procedures do not satisfy the requirements of Section 505(e), the APA, and the Due Process Clause with respect to withdrawal of NDAs. For example, the Citizen Petition procedures do not require any notice and leave the question of a hearing to the Commissioner's discretion. See 21 C.F.R. §§ 10.30(e), (h). The stay procedures require neither notice nor a hearing. See 21 C.F.R. § 10.35. In addition, although a Citizen Petition allows the petitioners to set forth any basis for the action requested, a withdrawal under Section 505(e) can be based only on the statutory criteria. Compare 21 C.F.R. § 10.30(b) (describing content of statement of grounds in a petition) with 21 U.S.C. § 355(e) (specifying the findings that must support withdrawal). The criteria for a stay are not

the same as the statutory criteria for withdrawal. Compare 21 C.F.R. § 10.35(e) with 21 U.S.C. § 355(e). No regulation issued by an administrative agency can confer on it any greater authority than it has under statute. Ass'n Am. Physicians and Surgeons v. FDA, 226 F. Supp 204, 216 n.17 (D.D.C. 2002) (citing Office of Consumers' Counsel v. FERC, 655 F.2d 1132, 1149 n.32 (D.C. Cir. 1980)). For this reason, FDA's regulations cannot confer authority to revoke an NDA by granting a Citizen Petition or an administrative stay of an approved NDA when the effect would be to accomplish a withdrawal of the approval in derogation of the procedural and substantive rights accorded by Section 505(e), the APA, and the Due Process Clause.

III. Petitioners cannot satisfy the criteria for a stay under 21 CFR § 10.35

A. Petitioners Request For a Stay Was Not Timely Filed

A request for a stay "must be submitted...no later than 30 days after the date of the decision involved." 21 C.F.R. 10.35(b). A petition for a stay of action submitted later than 30 days after the date of the decision involved "will be denied as untimely" unless the Commissioner permits a late filing, id. at § 10.35(g), an act the Commissioner may take only for "good cause." Id. at § 10.35(b).

This Petition was not submitted until nearly two years after the date FDA approved the Mifeprex NDA. Petitioners make no attempt to demonstrate good cause for permitting such a belated filing and no exception to the 30-day requirement is warranted in this case.

On the same day FDA approved the NDA for Mifeprex, it posted on its web site detailed information about the drug and the approval process, including the approval letter, copies of the approved labeling, including the package insert, the Patient Agreement, the Prescriber's Agreement, and the Medication Guide, information documenting the required reviews and approval action, questions and answers, etc. See, e.g., FDA Mifepristone Information; FDA Mifepristone Approval Package. Almost all of what the Petitioners are now

complaining of was known to the public on the day Mifeprex was approved, including FDA's analysis of the drug's efficacy as shown by clinical trials, FDA's analysis of the drug's safety, FDA's invoking Subpart H, and FDA's waiving the pediatric rule. Thus, petitioners could easily have lodged their request for a stay within the 30 days contemplated by FDA's regulations. There was no reason, surely no good cause, to wait an additional 22 months. This conclusion is not altered by the fact that a few issues raised by the Petitioners are based on documents FDA did not release until later and news reports about events occurring later. Petitioners should have filed their stay petition in October, 2000 and if necessary supplemented it with later-acquired information.

B. Petitioners Are Not Entitled to a Stay

Even had the Petition been timely filed, and even if FDA could bypass the law governing withdrawals and grant an administrative stay, no stay should be granted to Petitioners. FDA regulations require the Commissioner to issue a stay only if all the following requirements are satisfied:

1. The petitioner will otherwise suffer irreparable injury.
2. The petitioner's case is not frivolous and is being pursued in good faith.
3. The petitioner has demonstrated sound public policy grounds supporting the stay.
4. The delay resulting from the stay is not outweighed by public health or other public interests.

Id. at § 10.35(e). Petitioners have not met these requirements.

Petitioners fail at the first prong of the stay criteria, a showing of irreparable injury. The concept of legally cognizable injury to groups or associations has been well explored in the law. A mere interest in a problem, no matter how longstanding the interest and no matter how well versed in the problem an organization may be, cannot constitute injury in fact to the organization. Hunt v. Wash. State Apple Adv. Comm'n, 432 U.S. 333, 342 (1997); Warth v.

Seldin, 422 U.S. 490, 511 (1975); Gettman v. DEA, 290 F.3d 430, 434 (D.C. Cir. 2002). Though discussed in the context of standing, the applicability of this analysis to any definition of injury is obvious. The fact that a group or set of individuals may have a policy interest in how government regulates a certain product does not give rise to injury. Gettman, 290 F.3d at 434. Petitioners are interest groups opposed to abortion. Petition at 2. While claiming a general interest in women's health issues, id., the associations will derive neither benefit nor injury from FDA's regulation of Mifeprex. Nor have individual members claimed any injury. A legally cognizable injury to a person means that the injury must affect the person in a "personal and individual way." Lujan v. Defenders of Wildlife, 504 U.S. 555 560-61 (1992). See also Raines v. Byrd, 521 U.S. 811 (1997). As members of an association that opposes abortion, they cannot claim they will suffer any injury whatsoever arising from the availability of Mifeprex to others.

Petitioners fare no better under the other three stay criteria. With respect to the second criterion, their waiting nearly two years after approval of the NDA to mount this challenge calls into question their good faith in light of the fact that their arguments relate primarily to legal analyses and information that were accessible to them on the day of approval. On that day, September 28, 2000, FDA posted on its website detailed and substantial information about the approval and the standards the agency had applied. In fact, six of Petitioners' eight specific challenges relate to aspects of the approval that were complete at the time of approval and discussed in the documents posted on FDA's website at the time of approval. Petitioners' lack of diligence as to these six issues cannot be cured by their addition of two later-occurring issues.

The third and fourth criteria militate strongly against granting the petition. FDA did not treat Mifeprex any differently than it would have treated any other drug for which an NDA is submitted. FDA applied the same standards of safety and efficacy, the same kinds of

labeling requirements, and the same requirements for manufacturing as it applies to other drugs. FDA, CDER, Mifepristone Questions and Answers (Sept. 28, 2000), available at www.fda.gov/cder/drug/infopage/mifepristone-qa.htm ("The agency evaluates all drug applications submitted by sponsors to determine whether a drug is safe and effective for its proposed indication under the conditions of use in the labeling. This means that the benefits of the drug outweigh its risks. The same standards were applied to the new drug application for mifepristone as are applied to all applications.") (hereinafter "FDA Mifeprex Approval Q & A"). See also Senate Confirmation Hearing Questions and Answers for Dr. Mark McClellan, Final Set II at 13 (Oct. 2002) ("The Agency's review and approval of any drug adheres strictly to its statutory mandate and mission as a science-based public health regulatory agency.") (emphasis added). As discussed in detail below, Petitioners' challenges to FDA's regulation of Mifeprex fail because what FDA did was appropriate as judged under the statute, the science, and the standards FDA applies to all drugs. In these circumstances, it is not just Mifeprex, but FDA's regulation of all drugs that is under attack. Sound public policy militates in favor of continuing, not toppling, the regulatory structure FDA applies to all drugs, including Mifeprex.

Petitioners apparently are not content with FDA's regulating Mifeprex just as it regulates other drugs; they want FDA to impose restraints and constraints far beyond those applied to other drugs. Such disparate treatment is impermissible, Bracco, 963 F. Supp. at 27-28. In the case of Mifeprex, a drug for medical abortion, such overregulation - i.e., regulation beyond that required to secure the ends of the FDCA - is also constitutionally impermissible. Doe v. Bolton, 410 U.S. 179, 194 (1973) (invalidating restrictions on abortion that were "not based on differences that were reasonably related to the purposes of the Act in which it is

found") (citations omitted); Friendship Medical Center, Ltd. v. Chicago Bd. of Health, 505 F.2d 1141, 1152, 1153 (7th Cir. 1974) (same).

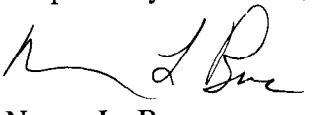
Sound public policy and public health considerations also require acknowledging that women exercising their constitutional right to choose abortion, Roe v. Wade, 410 U.S. 113 (1973), should be provided with the maximum number of choices among safe and effective means of accomplishing an abortion once they have chosen an abortion. Mifeprex is the only drug routinely used for medical abortion which has undergone FDA review and approval for safety and efficacy, and sound public policy surely favors continued availability of FDA-approved therapies. Although other means of abortion such as surgery are also safe and effective, some means women have traditionally been forced to use are not. The more FDA-approved options for abortion that are available, the smaller the chances that women will have to turn to unsafe or ineffective alternatives.

For the reasons discussed above, the Commissioner cannot make the finding that a stay is in the public interest and in the interest of justice. 21 C.F.R. § 10.35(e)(3). FDA itself and the sponsors of the Mifeprex NDA adhered scrupulously to the legal and scientific requirements which the Food, Drug, and Cosmetic Act imposes on the review and approval of New Drug Applications. Staying the approval, which would have the effect of reversing FDA's decision without the notice, opportunity for hearing, and substantive findings required by the FDCA, the APA, and the Due Process Clause is neither just nor a contribution to the public interest in the review of new drugs generally and Mifeprex specifically. The public interest is best served by FDA's following the law. Bracco, 963 F. Supp. at 30.

Conclusion

FDA's decision to approve Mifeprex was correct, and nothing has occurred in the intervening 29 months which allows or requires FDA to reverse its decision. The Petition must be denied for the reasons set forth above.

Respectfully submitted,



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