Exhibit G

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 10, 2013
Drug Name(s):	Mifeprex (mifepristone) 200 mg tablets
Therapeutic Class:	progesterone-receptor modulator
Dosage and Route:	Mifepristone 600 mg as a single oral dose followed by misoprostol 400 micrograms on Day 3
Application Type/Number:	NDA 020687/Danco Laboratories
(b) (6) #:	(b) (4) 2012-1287

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

EXECUTIVE SUMMARY

This review evaluates if the risk evaluation and mitigation strategy (REMS) for Mifeprex (mifepristone 200 mg tablets) continues to be necessary to ensure the benefits of the product outweigh its risks.

Mifeprex was approved on September 28, 2000 with a restricted distribution program requiring prescribers attest that they are knowledgeable about the safe and appropriate use of Mifeprex. The program was approved as a REMS on June 8, 2011. The goals of the REMS are:

- To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
- To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.

Since the approval of Mifeprex, safety concerns have been reported by certified prescribers, including serious infection and hemorrhage sometimes leading to the need for transfusions, hospitalization, and death. We reviewed the current Mifeprex safety data and researched what factors may affect its safe use for patients. Our key findings include that:

- The overall safety profile of Mifeprex has not changed over the last 6-7 years and is consistent with current product labeling.
- There have been a small number of serious complications associated with Mifeprex reported and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, and proper patient counseling.
    - Planned Parenthood and other family planning clinics account for the majority of Mifeprex use. Planned Parenthood implements the REMS requirements (b) (4).

Accurate gestation dating, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important components to ensure the safe use of Mifeprex in order to maintain the current safety profile. Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assuring safe use of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events. For these reasons, we believe the Mifeprex REMS provides the foundation to ensure the implementation of these safe use conditions with Mifeprex use.

(b) (6) therefore recommends that the existing elements of the REMS be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare settings provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population.

INTRODUCTION

This review evaluates if the risk evaluation and mitigation strategy (REMS) continues to be necessary to ensure the benefits outweigh the risks for Mifeprex (mifepristone 200 mg tablets).

(b) (4)

During a (b) (6) meeting on October 4, 2012[2], the Center Director requested that the REMS for Mifeprex be re-evaluated to determine if a REMS continues to be necessary to ensure that the benefits outweigh the risks, (b) (4)

The merits of (b) (4) for mifepristone 200 mg is addressed in a separate memorandum.

1 BACKGROUND & REGULATORY HISTORY OF MIFEPREX REMS

On September 28, 2000, Mifeprex was approved for the medical termination of intrauterine pregnancy through 49 days' gestation under 21 CFR 314.520 Subpart H.[3] According to the September 28, 2000 (b) (6) review, "the success of medical termination of pregnancy decreased with advancing gestational age and incidence of adverse events increased with advancing gestational age." In addition, the review states that timely access to medical care to manage serious complications is necessary. The (b) (6), 's approval memo states, "[t]he 1996 advisory committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregnancies (and other requirements), goals of safe and appropriate use may be achieved."[4]

As a result, FDA concluded Mifeprex must be available only through a restricted distribution program and required the program under Subpart H.

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1 (b) (4) (b) (4)

2 (b) (4), (b) (6)

3 Mifeprex Approval Letter signed September 28, 2000.

4 (b) (6) (b) (6) Memo. Signed September 28, 2000.

In 2007, Congress amended the FD&C Act to give FDA the authority to require a REMS when necessary to ensure that the benefits of a drug outweigh its risks.[5] Mifeprex was included on the list of products deemed to have in effect an approved REMS.[6]

The Mifeprex restricted distribution program was approved as a REMS on June 8, 2011 and contains the following elements:[7, 8]

A. Goals

- To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
- To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.

B. Medication Guide

C. Elements to Assure Safe Use, including:

a. Healthcare providers who prescribe Mifeprex will be specially certified by agreeing or attesting to the conditions set forth in the Prescriber Agreement.

b. Mifeprex will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

c. Mifeprex will only be dispensed to patients with documentation of safe use conditions.

D. An Implementation System that requires Danco to:

a. Certify distributors. To become certified, distributors must agree to:

i. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

ii. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

b. Assess the performance of the certified distributors with regard to the following:

i. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

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[5] Food and Drug Administration Amendments Act (FDAAA) of 2007, Pub. L. No. 110-85, Title IX, Subtitle A, Section 901, 121 Stat. 823 (2007).

[6] See Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313 (Mar. 27, 2008).

[7] Memorandum of meeting minutes for April 28, 2011 meeting between Danco and FDA. Signed by (b) (6) on June 3, 2011.

[8] Mifeprex REMS Approval Letter. Signed by (b) (6) on June 8, 2011.

ii. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

c. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

E. A Timetable for Submission of Assessments that requires Danco to submit REMS assessments to FDA one year from the date of approval of the REMS and every three years after.

The next REMS assessment is due June 2015.

2 SAFETY PROFILE OF MIFEPREX

2.1 BACKGROUND

Abortion is one of the most common procedures undergone by women of reproductive age in the United States.[9] Since 1969, the Centers for Disease Control and Prevention (CDC) has conducted abortion surveillance to document the number and characteristics of women obtaining legal, induced abortions. The 2009 data is the most recent year available. The CDC requests data from 52 reporting areas (i.e., 50 states, District of Columbia, and New York City). The areas provide information voluntarily; 45 areas reported data every year from 2000 – 2009. In most states, collection of abortion data is facilitated by the legal requirements for hospitals, facilities, and physicians to report abortions to a central health agency. These health agencies in turn voluntarily provide aggregate data to the CDC. For medical abortions, the CDC abortion surveillance summary does not include specific information on what medications and dosages are used.

A total of 784,507 abortions were reported to the CDC for 2009. Approximately 17% (16.2% ≤ 8 weeks' gestation, 0.9% >8 weeks' gestation) of abortions were reported as medical.[10,11] This is a slight increase from 2008 data (14.1% ≤ 8 weeks' gestation, 0.7% >8 weeks' gestation).[12]

In 2009, most (64.0%) abortions were performed at ≤8 weeks' gestation, and 91.7% were performed at ≤13 weeks' gestation. Among areas that reported data every year during 2000 – 2009, the percentage of abortions performed at ≤ 8 weeks' gestation increased 12% from 2008 to 2009.

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[9] Jones K et al. Abortion in the United States: Incidence and access to services, 2005. Perspect Sex Reprod Health 2008;41(1): 6-16.

[10] "the administration of medication or medications to include an abortion; at ≤8 weeks' gestation, typically involves the use of mifepristone and misoprostol; at >8 weeks' gestation, typically involves the use of vaginal prostaglandins". CDC does not report on specific medications and dosages used.

[11] Pazol K et al. Abortion Surveillance – United States, 2009. MMWR Surveillance Summaries 2012;61:1-44. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6108a1_htm?s_cid=ss6108a1_w#Tab24.

[12] Pazol K et al. Abortion Surveillance – United States, 2008. MMWR Surveillance Summaries 2011;60:1-40. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6015a1_htm?s_cid=ss6015a1_w.

2.2 SERIOUS COMPLICATIONS ASSESSED THROUGH THE REMS

Serious complications[13] assessed through the Mifeprex REMS include:

1. Hospitalizations
2. Transfusions of 2 or more units of packed cells or whole blood or having a hemoglobin of 6 gm/dL or less or a hematocrit of 18% or less
3. Serious infection, sepsis
4. Death
5. Other serious and unexpected adverse events

As of October 31, 2012, approximately 1.88 million women in the U.S. have been treated with Mifeprex for termination of pregnancy with 2,740 adverse events reported cumulatively (14 deaths, 768 hospitalizations, 66 ectopic pregnancies, 416 reports of blood loss requiring transfusion, and 308 infections [57 severe]). The overall estimate of a hospitalization over time is 1 in 2,448 patients. The following tables provide an analysis of the reporting rates of these adverse events over time.

Table 1 provides US Mifeprex use and adverse reporting rates per 100,000 uses in 2-year time intervals over the past 6 years (October 2006 through October 2012).

[13] Although ongoing pregnancies (confirmed and unconfirmed) are assessed in REMS assessment reports, ongoing pregnancy is not considered a serious complication because it usually reflects an incomplete abortion which is sometimes part of the medical abortion process.

Table 1: US Reporting Rates for Serious Adverse Events with Mifeprex per 100,000 uses from October 2006 through October 2012

Time Period	Use	Adverse events	Deaths	Hospital-izations	Trans-fusions	Ectopic Pregnancies	Infection	Severe[14] Infection
10/06 to 10/08	(b) (4) K*	357	1	105	63	9	48	8
Rate per 100 K	NA	(b) (4)						
10/08 to 10/10	(b) (4) K	600	4	187	103	18	71	10
Rate per 100 K	NA	(b) (4)						
10/10 to 10/12	(b) (4) K	704	0	213	115	11	67	17
Rate per 100 K	NA	(b) (4)						

NA= not applicable
*K = 1,000; for example, (b) (4) K = (b) (4). All rates are per 100,000 uses of the drug.
Source: the data here is extracted directly from the quarterly FDA reports using the same categories.

Table 2 provides an adverse event analysis for the most recent 18 months of available data from April 30, 2011 through October 31, 2012.

[14] This category includes endometritis (involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as Chlamydia infections and gonorrhea, cystitis and women with toxic shock syndrome not associated with a pelvic infection.

Table 2: Adverse Event Analysis - per (b) (6) US Postmarketing Adverse Event Summary from April 30, 2011 through October 31, 2012.

Time Period	~ # Women*	AEs reported	Deaths	Hospitalizations	Trans-fusions	Infections (severe)	Hospitalization Rate per women
4/30/11-10/31/11	(b) (4)	178	0	66	27	13 (5)	1 hospitalized per (b) (4) women
10/31/11 - 4/30/12		185	0	52	26	14 (3)	1 hospitalized per (b) (4) women
4/30/12-10/31/12		170	0	38	24	15 (1)	1 hospitalized per (b) (4) women

*Estimate based on above table showing (b) (4) U.S. women per month being treated with Mifeprex for termination of pregnancy from Feb 2011 through Oct 2012.

DEATHS

An overview of each of the US reports with a fatal outcome following mifepristone use for termination of pregnancy from approval in 2000 through January 9, 2013 is provided in Appendix A. Fourteen deaths in US women have been reported since approval. The last reported death occurred in March 2010. In half of the reported deaths, the cause of death was related to infection/sepsis. Two deaths were related to a ruptured ectopic pregnancy. Mifeprex is neither indicated for nor effective for terminating ectopic pregnancy.[15]

3 MIFEPRISTONE USE

3.1 MIFEPREX (MIFEPRISTONE 200MG TABLETS) UTILIZATION

Drug use information is not available to FDA through commercial databases for drugs distributed through closed distribution systems. Sales distribution data for Mifeprex is only available from the sponsor (Danco). Danco provides an estimate of the number of women who have used mifepristone in the US for termination of pregnancy on a periodic basis and as part of the REMS assessment. The (b) (6) has summarized the use data along with adverse event reporting information on a quarterly to semi-annual basis. A version of this document is available on FDA.gov (last report posted - April 2011).[16] The table below is based on the use data provided by Danco and documented in the (b) (6) summaries.

[15] "Mifeprex is contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies." Mifeprex [package insert] New York, NY. Danco Laboratories, LLC;2005.

[16] Available at http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323 htm 222. Accessed January 27, 2013.

Table 3: Estimate of the number of women who have used mifepristone in the US for termination of pregnancy per month				
End of Month/Year	Cumulative number of women from approval	Change	Number of Months	N/month
Mar 2006	575,000			
June 2006	612,000	37,000	3	12,300
May 2007	750,000	138,000	11	12,500
Jan 2008	855,000	105,000	8	13,100
Sept 2008	979,000	124,000	8	15,500
May 2009	1,100,000	121,000	8	15,100
Dec 2009	1,230,000	130,000	7	18,600
July 2010	1,350,000	120,000	7	17,100
Jan 2011	1,460,000	110,000	6	18,300
April 2011	1,520,000	60,000	3	20,000
Aug 2011	1,600,000	80,000	4	20,000
Dec 2011	1,680,000	80,000	4	20,000
Oct 2012	1,880,000	200,000	10	20,000

Danco states that the majority of drug/use ([(b) (4)]%) is distributed to/by Planned Parenthood and other family planning clinics. The remainder is distributed through hospitals and private practices. An independent study published in 2009 found 88% of Mifeprex for abortions was dispensed through clinics.[17]

3.1.1 Korlym (mifepristone 300mg tablets)

Korlym was approved without a REMS by FDA on February 17, 2012 for the treatment of Cushing's syndrome. However, the sponsor distributes Korlym through a single specialty pharmacy and agreed to provide use data as part of a PMR "to better characterize the incidence rates of adverse events with Korlym." Preliminary data from the first 6 months of marketing of Korlym indicated that [(b) (4)] patients under the care of [(b) (4)] prescribers received Korlym. Most of the use ([(b) (4)] of [(b) (4)] patients) was for the treatment of Cushing's syndrome. [(b) (4)]

[17] Finer L, Wei J. Mifepristone and abortion access in the U.S. Obstet Gynecol 2009;114:623-40.

(b) (4) Additional information on the (b) (4) code is pending.

3.2 FACTORS AFFECTING SAFE USE OF MIFEPREX

3.2.1 REMS

As described in Section 1.1, in order to obtain Mifeprex, healthcare providers must be willing to enroll in the REMS program by attesting to have the necessary skills and agreeing to comply with the program requirements. Based on the May 30, 2012 REMS Assessment submission, the following prescriber data were provided by Danco:

- Cumulative number of prescribers enrolled
- Number of new prescribers enrolled during reporting period
- Number of prescribers ordering Mifeprex during reporting period

(b) (4)

According to a study published in 2009 by Finer and Wei, between November 2000 and May 2007, among physicians who had ever provided mifepristone, 67% were obstetrician-gynecologists and 13% were family practice physicians.[17] Danco does not collect practice specialty information.

3.2.2 Planned Parenthood

Planned Parenthood and other family planning clinics account for the majority (e.g., (b) (4)) of Mifeprex use. Planned Parenthood has implemented (b) (4)

(b) (4)

[18] Fjerstad M, et al. Rates of Serious Infection after Changes in Regimens for Medical Abortion. NEJM. 2009;361-145-51.

Fjerstad et al performed a retrospective analysis assessing the rates of serious infection in the US after medical abortion. The rate of serious infection after medical abortion declined by 93% after these changes were implemented (from 0.93 per 1000 to 0.06 per 1000).[18]

In 2007, FDA stated that there was not "sufficient information to recommend the use of prophylactic antibiotics for women having a medical abortion." The current American College of Obstetricians and Gynecologists Practice Bulletin on medical abortion states that "no data exist to support the routine use of preventative antibiotics for medical abortion." The Practice Bulletin recommends oral or vaginal administration of misoprostol.[19]

The current Mifeprex professional labeling does not include information on antibiotic prophylaxis and does recommend oral (as opposed to vaginal) administration of misoprostol (in a dose different from current standard practice outlined in the ACOG Practice Bulletin and Planned Parenthood protocol).

3.2.3 Physician Training in Induced Abortion[20,21,22]

In 1996, in response to data indicating that the (1) age of practicing obstetricians who provided the majority of pregnancy terminations was rising (older than 65 years) and (2) the majority of counties in the U.S. lack of abortion providers, the Accreditation Council for Graduate Medical Education (ACGME) required obstetrics and gynecology residency programs to provide training *opportunities* in induced abortion.

In 1998 and 2004, a survey was mailed to all obstetrics and gynecology residency program directors in an effort to characterize the availability of abortion training. In 1998, 46% of respondents reported routine[23] training. In 2004, 51% of directors reported routine training, 39% reported optional training, and 10% reported no training. Of those programs with routine training, 50% reported training in termination practices -- the most common were first-trimester surgical abortion (85%), followed by medical abortion (59%), second trimester induction (51%), and dilation and extraction (36%).[20]

A survey[22] conducted in 2007 of final year obstetrics and gynecology residents sought to determine which abortion procedures residency graduates had received training. Respondents reported higher routine, on-site participation in training on surgical abortion procedures (range 65.6% - 85.2%) compared to mifepristone (52.3%). Routine participation in off-site mifepristone training was higher (72.7%). Ten percent of respondents reported that no training was available on mifepristone use, which is consistent with the 2004 study of residency program directors.

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[19] ACOG Practice Bulletin: *Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 µg of misoprostol vaginally are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.*

[20] Eastwood KL, et al. Abortion training in United States obstetrics and gynecology residency programs. Obstet Gynecol 2006;108;303-8.

[21] Greenberg M. et al. Barriers and enablers to becoming abortion providers: the reproductive health program. Fam Med 2011;44(7):493-500.

[22] Jackson CB, Foster AM. Ob/Gyn training in abortion care: results from a national survey. Contraception 2012;86:407-417.

[23] Routine training was defined as "required training unless residents express moral objections."

The ACGME requirements for family medicine residents do not include training in medical abortion but residents must be "trained to competency" in "options counseling for unintended pregnancy." A similar survey to characterize the availability of abortion training in family medicine residencies reported 49% provide some type of abortion training.

From 1999 through 2005, the Department of Family Medicine at the University of Rochester Medical Center operated the Reproductive Health Program (RHP), a national elective abortion training program aimed to address a gap in training to all US medical students, residents, advanced practice clinicians, and physicians in practice. A study published in 2012 interviewed RHP trained providers in 2008-2009. A total of 58.8% of respondents reported providing abortions since training, with most occurring in high-volume abortion clinic settings. Of those who had provided abortions, most had performed more than 50 surgical or medical abortions. More than 90% of abortion providers reported having liability insurance that covers abortion, colleague support, ease of obtaining medications and/or equipment, reimbursement, and administrative and/or staff support at the site where they provide abortions. Relative to providers, the greatest barriers to providing an abortion reported by non-providers were lack of skills, concerns about liability, and difficulty obtaining supplies.[21] Although these data were limited to RHP trainees, data are consistent with data from other sources and provides additional insight into what facilitates abortion care and barriers.

4 CONSIDERATIONS REGARDING THE NEED FOR A REMS

4.1 SAFETY CONSIDERATIONS

In general, the intended patient population for Mifeprex is healthy. Medical abortion, similar to surgical abortion, is associated with potentially serious adverse events. Since the approval of Mifeprex, safety concerns have been identified through enhanced surveillance and reporting by certified prescribers. Use of Mifeprex is associated rarely with serious infection and hemorrhage sometimes resulting in transfusions, hospitalization, and death. Serious infections and deaths resulted in labeling changes in 2004 and 2005. There have been no new safety concerns identified with Mifeprex since that time and the serious complications being reported now are consistent with labeling. Moreover, these complications with Mifeprex are consistent with what one can expect with spontaneous abortion and surgical abortions.[24,25] The serious complications that arise can be managed if recognized in a timely manner.

(b) (6) believes that the current safety profile is reflective of an effective system in place with knowledgeable prescribers primarily using Mifeprex within that system guided by standard protocols. It is not likely that the current safe use conditions will persist to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events if the REMS was eliminated. Because Mifeprex prescribing occurs in a limited number of healthcare settings and training is not uniformly provided in physician residencies, there is no data

[24] Mifeprex [package insert] New York, NY. Danco Laboratories, LLC;2005.

[25] Grimes, DA and Raymond, EG. Medical Abortion in Adolescents, *BJM* 2011;342:d2185.

indicating that the appropriate use of Mifeprex has become an ingrained part of "standard medical practice". The "standard" is for Mifeprex to be prescribed within these family planning clinics or by qualified physicians in a private setting. However, if the REMS is eliminated, use would no longer be restricted to these practice settings with knowledgeable prescribers, and use outside the current effective "standard practice " setting could occur.

If the REMS for Mifeprex is eliminated, there would be no restrictions for dispensing and Mifeprex (or any generics that may be approved in the future) could be made available (depending on the manufacturer's business decisions) in the same manner as any prescription drug product. Such a change could result in 1) treatment delays which are problematic given the importance of gestational timing on the safe and effective use or 2) inappropriate prescribing (e.g., ectopic pregnancy) by less experienced practitioners.

4.2 MONITORING CONSIDERATIONS

It is not known how adverse event reporting will change if a REMS is eliminated. Planned Parenthood and the manufacturers would not be required to continue the same level of reporting of serious complications. Data on deaths from infection after Mifeprex use would be available through the CDC. The CDC conducts regular surveillance for maternal mortality and morbidity associated with pregnancy and abortion, including deaths from infection following a medical abortion or any pregnancy event. We note the abortion surveillance summaries published by CDC can have a lag time of up to four years.

Reporting may not be important if it was determined that the risks no longer warrant additional safe use requirements. However, given the public interest this medication generates, it is likely information inquiries will continue. If the REMS is eliminated, FDA will be less informed of adverse events that occur with Mifeprex or its generics.

4.3 DISTRIBUTION CONSIDERATIONS

The [redacted] (b) (6)) believes that Danco would continue some sort of restricted distribution even if FDA no longer requires it. It is not known how new generic sponsors/manufacturers would choose to distribute mifepristone if no restrictions were required by FDA. Even if not required and both innovator and generic manufacturers choose to continue to dispense mifepristone through clinics and medical offices, this would be based on the various manufacturers business decisions and subject to change at their discretion.

Without a REMS, prescriber and patient usage information may be more complex to obtain and less precise than the current data. Furthermore, if the sponsor(s) chose to maintain a closed distribution system, it would be difficult for FDA to track use data in the absence of being provided data directly from the sponsor(s).

4.4 CONFIDENTIALITY/PRIVACY

Confidentiality and patient privacy are significant issues with Mifeprex, but not generally a factor when determining the need for a REMS. The availability of Mifeprex through retail pharmacies could reduce patient/prescriber confidentiality by adding the need to write and fill a prescription. Concerns regarding protests or targeting may deter retail pharmacies from stocking Mifeprex.

The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. While we remain concerned about confidentiality and concerned regarding the personal safety of the prescribers, pharmacists, and patients, it does not meet the criteria for requiring a REMS. Moreover, manufacturers could decide to protect prescriber and patient confidentiality without a REMS.

5 IMPACT OF REMS ELEMENTS AND THEIR REMOVAL

The risk mitigation tools that are part of the Mifeprex REMS are physician certification and controlled access (or restricted distribution). A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safely and appropriately. A prescriber self-certifies by completing a one-time enrollment form. This enrollment or certification requirement is the tool that provides controlled access to Mifeprex. Without restricted distribution, a prescriber using Mifeprex would not have to attest to having certain skills, agree to provide counseling on how to handle adverse events, provide Mifeprex during the office visit, document certain information/activities, or report serious complications.

5.1 PRESCRIBER CERTIFICATION

This Prescriber Agreement is a one-time event with limited burden. Prescriber certification probably has the most influence of the three ETASUs in addressing safe use and limiting access to Mifeprex because this element requires physicians to attest to having certain skills, agree to abide by the program requirements including reporting of serious adverse events, and complete an additional step (e.g., the enrollment form) in the usual drug procurement process.

Eliminating this element opens access to any prescriber. Therefore, it is possible that physicians and advanced practice healthcare providers (e.g., physician assistants, nurse practitioners) who are not familiar with Mifeprex and/or practice outside of facilities with established protocols may prescribe Mifeprex; a factor that could contribute to an increase in serious complications.

5.2 RESTRICTED TO CERTAIN HEALTHCARE SETTINGS

This element limits distribution by preventing the distribution of Mifeprex through retail (including mail order and internet) pharmacies. If this restriction was removed, any pharmacy could stock the drug and prescribers would no longer have to stock Mifeprex. In a "worst case" scenario, the following *could* occur:

- patients are not properly counseled about the serious complications and what to do in the event that they experience an adverse event,
- patients may not pick-up the prescription – failing to initiate the abortion in a timely manner resulting in ineffective or inappropriate use of the drug or potentially an increased incidence of complications,
- patients have difficulty finding a pharmacy that stocks the drug because not all pharmacies may choose to stock the drug, resulting in treatment delay

Although not safety concerns, confidentiality and personal safety are significant concerns with Mifeprex. Distribution through retail pharmacies could compromise patient and

prescriber confidentiality with adding a new stakeholder to the treatment process, and pharmacies could be targeted by individuals or groups opposed to abortions.

Restriction of mifepristone to certain healthcare settings is probably the most critical element for maintaining confidentiality and privacy for both patients and prescribers. This element also contributes to the patient's safe use of Mifeprex by making the prescriber responsible for giving the drug directly to the patient and counseling the patient at the time of dispensing. It is safer for the patient - providing the opportunity for direct observed therapy (although this is not a REMS program requirement) to initiate the time-sensitive abortion process, and ensures the patient leaves the healthcare facility with the medications that are necessary for completing a medical abortion to maximize efficacy and minimize risk.

5.3 DOCUMENTATION OF SAFE USE CONDITIONS

The REMS requires that prescribers review and complete a Patient Agreement with each patient before treatment is initiated. The signed Agreement is placed in the patient's medical record; however it is not collected by Danco. There is no data available on how often the Agreement is utilized.

Family planning clinics generally utilize consent forms and in this type of practice setting the Patient Agreement may be redundant. Therefore, it is not known if removing this element would increase the risk that a patient is not properly informed and counseled about complications and what to do when a complication occurs.

6 DISCUSSION

(b) (6) and (b) (6) considered two options – maintain the REMS or eliminate the REMS with the following possible rationale for each option.

- Eliminate the REMS: No new safety concerns have been identified in 6 - 7 years. The serious complications being reported now have been consistent with labeling and the reporting rate has been stable over the last several years. These complications are consistent with what one would expect with a surgical abortion and are not necessarily unique to a medical abortion with Mifeprex. Use of Mifeprex has been primarily in Planned Parenthood and other family planning clinics where there are protocols and familiarity with assessing the duration of pregnancy, diagnosing an ectopic pregnancy, performing surgical interventions in cases of incomplete abortion, and caring for patients that experience serious complications. Some of the safe use practices surrounding Mifeprex may therefore already be embedded in these practice sites that already dispensing Mifeprex and would likely be maintained even if the REMS were eliminated.

- Maintain the REMS: There have been a small number of reported serious complications associated with Mifeprex and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, proper patient counseling, and follow-up procedures.

  Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and

experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assuring safe use of Mifeprex.

The Mifeprex REMS provides the foundation to ensure the implementation of safe use conditions with Mifeprex use. Accurate gestation dating, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important to maintaining the current safety profile of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events.

7 RECOMMENDATION AND CONCLUSION

(b) (6) recommends that the existing elements of the REMS should be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare settings provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population.

On January 30, 2013, (b) (6) and (b) (6) presented this recommendation to the Center Director and senior level management from (b) (6) There was general consensus that a REMS is necessary to ensure that the benefits outweigh its risks.

Appendix A: Overview of US Mifeprex Cases with Fatal Outcomes

State	Date of Death	Patient Age	Cause of Death	Culture if Available
(b) (6)		38	Hemorrhage from ruptured ectopic pregnancy	N/A
		18	Septic shock	CDC positively identified *C. sordellii* in uterine tissue
		21	Presumed infection	CDC positively identified *C. sordellii* in uterine tissue
		22	Sepsis	CDC positively identified *C. sordellii* in uterine tissue
		34	Sepsis	CDC positively identified *C. sordellii* in uterine cavity
		32	Not specified^ (autopsy declined)	Uterine cavity culture positive for Prevotella and Peptostreptococcus
		23	Probably methadone overdose	N/A
		24	Septic shock	Probably *C. perfringens*
		22	Suspected homicide	N/A
		23	Cocaine and Fentanyl poisoning	N/A
		18	Septic shock & cardiac arrest	*C. sordellii* confirmed in uterine samples
		29	Complications due to acute endometritis & myometritis	CDC positively identified *C. sordellii* in uterine tissue
		21	Not specified, but presumed *C. sordellii infection*	CDC positively identified *C. sordellii*
		27	Ruptured ectopic pregnancy	N/A

[A]The (b) (6) death occurred on (b) (6) (Day 33) after an initial failed surgical and medical abortion on (b) (6) (Day 1) in a woman with a large uterine fibroid. A repeat surgical abortion was done on (b) (6) (Day 22). We do not believe the death was related to the attempted medical abortion on (b) (6).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

10/17/2013

(b) (6)

10/17/2013

Received concurrence from (b) (6)